PAIN MEASUREMENT AND MANAGEMENT IN ELDERLY PATIENTS

CLINICAL STUDIES IN LONG TERM HOSPITAL CARE AND AFTER CARDIAC SURGERY

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I Kauppila T, Pesonen A, Tarkkila P, Rosenberg PH. Cognitive dysfunction and depression may decrease activities in daily life more strongly than pain in community-dwelling elderly adults living with persistent pain. Pain Practice 2007; 7: 241-47.

II Pesonen A, Kauppila T, Tarkkila P, Sutela A, Niinistö L, Rosenberg PH. Evaluation of easily applicable pain measurement tools for the assessment of pain in elderly and demented patients. Acta Anaesthesiol Scand 2009; 53: 657-64

III Pesonen A, Suojaranta-Ylinen R, Tarkkila P, Rosenberg PH. Applicability of tools to assess pain in elderly patients after cardiac surgery. Acta Anaesthesiol Scand 2008; 52: 267-73.

IV Pesonen A, Suojaranta-Ylinen R, Hammarén E, Tarkkila P, Seppälä T, Rosenberg PH. Comparison of opioid effects and plasma concentrations of fentanyl and oxycodone between elderly and middle-aged patients after cardiac surgery. Acta Anaesthesiol Scand 2009; 53: 101-8.

V Pesonen A, Suojaranta-Ylinen R, Hammarén E, Kontinen V, Raivio P, Tarkkila P, Rosenberg PH. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: A randomized placebo-controlled trial. Br J Anaesth 2011; 106: 873-81.

2. ABBREVIATIONS AND ACRONYMS

ANOVA	Analysis of variance
BIS	Bispectral Index
GABA	Gamma-aminobutyric acid
CABG	Coronary artery bypass grafting
CAM-ICU	Confusion of assessment method for the intensive care unit
CPB	Cardiopulmonary bypass
CR	Controlled release
CRPS	Complex regional pain syndrome
CYP_{450}	Cytochrome P 450
DSM-IV	Diagnostic and statistical manual of mental disorders
FPS	Face pain scale
GC-MS	Gas chromatograph-mass spectrometer
GDS	Geriatric depression scale
GRS	Graphic Rating Scale
ICU	Intensive care unit
i.m.	Intramuscular
IQR	Inter-quartile range
IR	Immediate release
i.v.	Intravenous
MMSE	Mini-mental state examination test
MPQ	McGill Pain Questionnaire
MSTFA	N-methyl-N-trimethylsilyl-trifluoroacetamide
NS	Not significant
PAINAD	Pain Assessment IN Advanced Dementia
PQ	Finnish version of McGill Pain Questionnaire
RASS	Richmond Agitation- Sedation score
RWS	Red wedge scale
SD	Standard deviation
VAS	Visual analogue scale
VRS	Verbal rating scale

3. ABSTRACT

The proportion of patients over 75 years of age, receiving all different types of healthcare, is constantly increasing. The elderly undergo surgery and anaesthetic procedures more often than middle-aged patients. Therefore, clinical trials in the older category of patients will be needed to facilitate improvements in health care methods. Pain is commonly underestimated in the elderly during the postoperative period and also during rehabilitation in the geriatric department of a primary care hospital. Pain management should be based on regular pain assessment with easily applicable and validated pain measurement tools. The aim of this study was to investigate pain measurement and management in cognitively impaired patients in long term hospital care and in cognitively normal elderly patients after cardiac surgery.

Studies I-V incorporated 366 patients, including 86 home-dwelling or hospitalized elderly (I-II) and 280 patients undergoing cardiac surgery (studies III-V). Patients suffered from chronic pain (studies I-II) or acute pain (studies III-V). Pain intensity was measured with the Verbal Rating Scale (VRS) (study I-V), the Visual Analogue Scale (VAS) (study I-III), the Red Wedge Scale (RWS) (study II-IV), and the Facial Pain Scale (FPS) (studies II-III). Cognitive function was assessed with the mini-mental-state examination (MMSE, 0 to 30) (studies I-II, V), depression with the Geriatric Depression Scale (GDS, 0 to 15) (studies I-II), and functional ability in daily life assessed with the Barthel Index (0 to 100) (study I). Postoperative sedation was assessed with the Ramsay sedation scale (study IV) and with the Richmond Agitation Sedation Score (RASS) (study V). The degree of postoperative confusion was measured with the modified Confusion Assessment Method for the ICU (CAM-ICU, 0 to 25) test (study V).

The effects and plasma concentrations of fentanyl and oxycodone were measured in elderly (≥ 75 years, n=30) and middle-aged patients (≤ 60 years, n=20) after cardiac surgery (study IV). Fentanyl plasma concentrations were measured at the end of surgery and two hours later. The blood samples for fentanyl and oxycodone plasma concentrations measurements were taken after tracheal extubation, when a threshold of pain intensity was reached (VRS ≥ 2). Thereafter, an intravenous 0.05 mg/kg dose of oxycodone was administered. Oxycodone plasma concentration, pain intensity, and the degree of sedation were determined 15 and 45 min after the oxycodone dose. This protocol was repeated twice in study IV.

The opioid-sparing effect of pregabalin was studied after cardiac surgery in elderly patients (≥ 75 years, n=70) whom were randomized to receive either placebo or pregabalin (150 mg) preoperatively followed by either placebo or pregabalin (75

mg) twice daily postoperatively (study V). When the pain intensity was elevated (VRS ≥ 2), patients received oxycodone either intravenously (0.05 mg/kg) or orally (0.10-0.15 mg/kg). Postoperative pain was assessed using the VRS, by a telephone interview, both one and three months after operation.

The mean age of patients was 77 (SD ± 8) years and 8364 pain measurements were performed with four pain scales in elderly patients (studies I-V). All pain scale measurements correlated positively with each other at rest and during movement (studies I-III). The Barthel Index correlated positively with MMSE scores (r = 0.367, P < 0.05) and negatively with GDS (r = -0.176, P < 0.05), but has no constant negative correlation with pain scores in study I. Patients with an MMSE more than 24, were able to use all four pain scales rather successfully. The VRS was most successful in the groups of demented patients (MMSE 17-23, 11-16 and ≤ 10) and in elderly patients (≥ 75 years) on the first day after cardiac surgery (study II-III). Success rates improved for all scales during the four postoperative days after cardiac surgery (study IV). The elderly had a higher plasma concentration of fentanyl at the end of cardiac surgery than younger (≤ 60 years) patients (P = 0.001). The plasma concentrations of oxycodone were comparable between the groups. Pain intensity on the VRS was lower at the 45 min assessment point after all three oxycodone tests doses (P = 0.008) and the sedation scores were significantly higher after the third dose of oxycodone in the elderly (P = 0.035) (study IV). Total oxycodone consumption from extubation to the end of the fifth postoperative day was reduced by 48% in the pregabalin group (P < 0.05; study V). The CAM-ICU scores were significantly lower on the first postoperative day in the placebo group (P < 0.05). There was no significant difference with respect to the MMSE scores or the RASS scores between the pregabalin and placebo groups. The incidence of postoperative pain during movement was significantly lower in the pregabalin group 3 months after surgery.

This investigation demonstrates that chronic pain did not seem to impair daily activities as much as cognitive dysfunction and depression in home-dwelling Finnish elderly people. The VRS appeared to be applicable for elderly patients with clear cognitive dysfunction (MMSE<17) and it was the most feasible pain scale for the early postoperative period after cardiac surgery. After cardiac surgery, elderly fentanyl plasma concentrations were elevated, although plasma oxycodone concentrations were at a similar level compared to middle-aged patients. The elderly had less pain and were more sedated after doses of oxycodone. The administration of pregabalin reduced postoperative oxycodone consumption after cardiac surgery. Pregabalin-treated patients had less confusion, in addition to less early postoperative pain on the first postoperative day and during movement at three months post-surgery.

4. INTRODUCTION

Pain may often be underrecognized and inadequately managed in the elderly. Previous studies have demonstrated that 25 to 50% of community-dwelling elderly report pain that interferes with daily life (Higgins *et al.* 2004; Thomas *et al.* 2004). Pain incidence rates of 45 to 80% have been reported for patients in long-term care facilities (Ferrell *et al.* 1990; Ferrell *et al.* 1995), although a study by Finne-Soveri and colleagues reported that 22 to 24% of residents experienced daily observable pain and this was most evident in the more disabled subjects (Finne-Soveri *et al.* 2000). Many studies have also documented an unacceptable prevalence of poor pain control after surgery (van den Bosch *et al.* 2006). Poorly controlled and acute pain can be severe, which can increase the risk of a chronic pain state (Bruce *et al.* 2003). Despite the fact that the measurement of pain intensity is difficult because it is multifaceted including affective, cognitive, physical, sensory, behavioral, social and cultural factors (McGuire 1992), pain measurement remains a critical first step to deliver effective and adequate pain management. Pain assessment in the elderly should start with self-reported pain, but also nonverbal pain behaviors should be evaluated among individuals with severe dementia or other conditions that impair communication (Fuchs-Lacelle and Hadjistavropoulos 2004; Fuchs-Lacelle *et al.* 2008).

Pain relief after surgery and for chronic pain can be improved by the routine assessment of pain intensity, and by the routine use of simple validated pain measurement scales for the elderly (Ferrell *et al.* 1995; Breivik and Stubhaug 2008; Breivik *et al.* 2008). The ability to achieve effective pain control with minimal adverse effects from analgesics is desirable in the elderly; there is a need for improved methods of assessing pain in older adults, especially those with postoperative confusion, cognitive impairment or dementia.

Opioids are the main drugs chosen to treat moderate to severe postoperative and chronic pain (Kalso 2005a; Wilder-Smith 2005; Breivik and Stubhaug 2008). Although the opioid dose should be individually tailored relative to the pain measured and serious side-effects like respiratory depression, sedation, and nausea are common problems in elderly pain management.

Therefore, new pain treatment strategies are needed for elderly patients. Multimodal analgesia has an important role for optimal pain treatment; it may decrease opioid consumption and also reduce opioid-related side-effects. Pregabalin is an anti-epileptic drug that has demonstrated anti-hyperalgesic properties in human pain models (Chizh *et al.* 2007). Pregabalin may be a useful drug for multimodal analgesia in pain management after cardiac surgery and in chronic pain in the el-

derly (Guay 2005; Tiippana *et al.* 2007; Gilron 2007).

The purpose of the present study was to evaluate pain assessment and to improve pain control in demented older adults in long-term hospital care and cognitively normal elderly patients after cardiac surgery. The goal was to investigate effects and plasma concentrations of fentanyl and oxycodone and the use of pregabalin for pain management after cardiac surgery.

5. REVIEW OF THE LITERATURE

Western countries, and indeed most parts of the developed world, have accepted that reaching the retirement age of 65 years defines someone as an elderly person. However, the age of 65 is often the beginning of old age in Finland and the classifications by age provide no information about a person´s health and physical condition. Elderly patients can be generally classified into a younger (age 65-75) and an older group (age 75 and over). The percentage of elderly aged 75 and over that receives institutional care or housing services for elderly was only at 10 per cent of the corressponding age group. There were 255 912 persons aged 80 and over in Finland´s population (5, 37 million) at the end of 2010. The number has increased five-fold over the last 40 years (Finland). According to the Official Statistics of Finland, 42 802 persons lived in residential homes for older people and sheltered housing units with 24-hour assistance at the end of 2009, where the average age was 83.7 years (National Institute for Health and Welfare 25/2010). The number of elderly surgical patients will be expected to increase to approximately 5.2% of the Finnish population by 2020. The majority of surgical procedures are performed in the elderly, whose function and better quality of life have improved significantly along with the advances in surgical technology and techniques.

5.1. ACUTE PAIN IN THE ELDERLY

The relationship between ageing and postoperative pain remains unclear despite a number of investigations. Many studies have suggested that elderly patients report lower pain intensity than younger patients (Bisgaard *et al.* 2001; Kalkman *et al.* 2003), whereas the others have not found age differences (Gagliese *et al.* 2000; Morin *et al.* 2000). However, even with developments in methods for assessing pain, elderly patients´ postoperative pain is often undertreated (Feldt *et al.* 1998; Aubrun *et al.* 2003; Aubrun and Marmion 2007; Breivik and Stubhaug 2008). Moreover, cognitively impaired older patients receive significantly less analgesics than cognitively intact elders undergoing similar painful surgical procedures (Morrison and Siu 2000), although there is no clinical evidence that cognitive impairment is associated with decreased pain intensity or sense (Gibson and Helme 2001). The studies of pain assessment and management practices for elderly patients with hip fractures admitted to acute care settings show that pain in this population still continues to be undermeasured and undertreated (Ardery *et al.* 2003a; Titler *et al.* 2003; Herr *et al.* 2004;). High postoperative pain intensities and undermedication

in the elderly are associated with postoperative pulmonary complications, postoperative confusion and delirium, increased hospital length of stay, and long-term functional impairment (Feldt and Oh 2000; Shea *et al.* 2002). Postoperative pain may cause suboptimal mobilization and medical complications because of immobility. Cardiovascular consequences of unrelieved pain include increased heart rate, blood pressure, and myocardial oxygen demand with an increased risk of myocardial infarction. The severity of perioperative and postoperative pain can also influence the development of postsurgical chronic pain syndromes such as sternotomy pain (Bruce *et al.* 2003; Lahtinen *et al.* 2006).

Numerous guidelines have been published relating to the management of postoperative pain. The Agency for Health Care Policy and Research (AHCPR) pioneered the education of caregivers, followed by the American Pain Society and the American Society of Anesthesia. More recently, the Joint Commission Accreditation of Healthcare Organizations (JCAHO) has published "Standards for Pain Management in Hospital Settings" that were implemented 2001.

5.2. CHRONIC PAIN IN THE ELDERLY

Chronic pain has been traditionally defined by pain duration, but this approach has limited empirical support. Chronic pain continues past the normal duration of tissue damage, that is usually more than 3-6 months (Gagliese and Melzack 1997). It can lead to functional loss, reduced daily activity and reduced quality of life, which in turn can also cause mood and behavior changes. Chronic postoperative pain is evident for one in ten surgical patients, developing to be an intolerable, CRPS-like, chronic pain condition after one of every hundred operations, irrespective of the type of surgery (Kehlet *et al.* 2006).

Chronic pain is very common and often underestimated and undertreated in the elderly, especially among old people living in nursing homes. Many studies show that 25 to 50% of older patients experience clinically relevant pain, and among nursing home residents the prevalence is 45 to 85%. Other studies show that about 80% of older patients suffer from a chronic disease typically associated with pain (Finne-Soveri and Tilvis 1998a; Won et al. 2004; AGS Panel on Persistent Pain in Older Persons 2002; Achterberg et al. 2010). Nevertheless, chronic pain is still rarely evaluated among nursing home residents and hospital patients, perhaps because of the common belief that aging and pain are conversely linked together. Consequently, depression, sleep disorders, anxiety, cognitive dysfunction, malnutrition, slow response to rehabilitation therapy, and immobility, which are common in the elderly, can be influenced by pain (Gallagher et al. 2000; Gloth 2000; Edwards et al. 2003). Chronic pain associates too often with surgery and the poor treatment of acute pain in the elderly (Won et al. 2004).

Neuropathic pain is a common type of chronic pain that is caused by pathology in the peripheral or central nervous system such as neuropathies, postherpetic and trigeminal neuralgias, and cerebrovascular strokes (Dworkin 2002; Jensen 2002). Neuropathic pain is highly diffuse, has a low response to analgesics, and is difficult to treat. A study from 68 United Kingdom nursing homes found a 37% prevalence of chronic non-cancer pain and a 2% prevalence of chronic cancer pain. Neuropathic pain is common in the elderly and its occurrence can be related to complex factors. A large number of factors and medical conditions are commonly associated with pain in long-term care residents (Ferrell et al. 1995; Allcock et al. 2002). In most cases, pain among the elderly is a common experience that is often characterized by the concomitant presence of different types of varying diseases and causes of pain at multiple locations.

5.3. ASSESSMENT OF PAIN IN ELDERLY PATIENTS

The assessment of older patients experiencing pain can be a challenging process in the different stages of clinical practice. The assessment of acute pain should be a simple and fast task for all patients, whilst the assessment of chronic pain presents a more demanding task (Herr and Garand 2001; Gagliese and Katz 2003; Rakel and Herr 2004). The assessment of chronic pain conditions requires pain history, physical examination, and specific diagnostic tests. The pain history must indicate location, intensity, pain descriptors, temporal aspects, pathophysiological and a etiological issues and the type of pain involved (nociceptive, neuropathic). Therefore, a comprehensive medical history is an important part of the pain history, including the consideration of reasons for a complex pain condition (Gagliese and Melzack 1997 Gallagher *et al.* 2000; Breivik *et al.* 2008).

An Interdisciplinary Expert Consensus Statement on Assessment of Pain in Older Persons (Hadjistavropoulos et al. 2007) is intended to provide recommendations that will be useful for both researchers and clinicians. Self-report pain assessment procedures have been accepted as the most reliable source of information on older patient's pain unless the patient has serious limitations in their ability to communicate. The majority of older patients are able to make a self–report regarding pain. However, it is not only important to allow the patient to have sufficient time to consider the questions and formulate answers, but also to explore different words that elderly patients may use synonymously with pain such as "ache,", "soreness," "bother" or "hurting". Pain assessment recommendations for older adults are presented in Table 1 by Rakel and Herr 2004. The assessment of chronic pain and the effects of treatment remain more challenging in patients suffering pain from non-cancer causes. Also many older patients suffer from both acute and chronic components

of pain in tandem, making it difficult to find a suitable, valid and reliable pain measurement tool in clinical practice. As with chronic pain, the assessment of acute pain should include an appropriate pain history, including the evaluation of pain intensity, location, character, and recent changes (Hadjistavropoulos et al. 2007).

Table 1. Summary of Pain Assessment Recommendations for Older Adults ***(Rakel and Herr 2004)***

1. Consider obvious sources of pain, including incisions, trauma, positioning, irritating infusions, and recent surgery.

   Consider the elder's history and potential chronic conditions that could be contributing to pain.
2. Attempt to obtain self-report of pain presence and pain intensity.

   Use simple questions and adapted instruments appropriate for elders and those with cognitive impairment.
3. For elders unable to self-report, use behavioral observations (both typical and less obvious) and physiologic indicators to support a suspicion of pain.
4. Use family members' or other caregivers' knowledge of the elder's baseline behaviour to identify changes in behavior or activities suggestive of pain.
5. Consider giving an analgesic dose and observe for changes in behaviour to validate suspicion of pain.
6. Systematically assess and document at regular intervals and after interventions have had time to take effect.
7. Use the same pain scale or behavioural approaches each time pain is assessed.
8. Record pain assessment data in accessible location available to all health providers involved in the elder´s care.

5.3.1. PROBLEMS WITH ADEQUATE ASSESSMENT IN THE ELDERLY

Many elderly people consider pain to be a normal part of aging. Furthermore, older patients may view pain as a normal part of surgical procedures as will some of their caregivers (McCarberg 2005). Reporting of pain can be influenced by cultural, social, physiological and psychological changes associated with aging. Addition-

ally, anxiety, fear, depression, cognitive impairment, confusion and postoperative delirium, dealing with the implications of disease, loss of independence, and feelings of isolation may all impact on the experience of the pain intensity (AGS Panel on Persistent Pain in Older Persons 2002; Davis and Srivastava 2003).

5.3.2. DOCUMENTING PAIN

The patient is the best and only reliable source for pain assessment (AGS Panel on Persistent Pain in Older Persons 2002; Brummett CM and Hasset AL 2011; Gilron I and Jensen MP 2011). If the patient is able to verbally communicate, they may provide a description of the quality, location and nature of the pain, in addition to factors that impact on pain relief or exacerbation. Cognitive impairment reduces the relative volume of reports of pain intensity and general pain complaints (Parmelee *et al.* 1993; Farrell *et al.* 1996; Parmelee 1996; Herr *et al.* 2006a).

5.3.3. PAIN INTENSITY MEASUREMENT TOOLS FOR THE ELDERLY

There is no universal pain assessment scale that is suitable for all older patients. However, pain assessment tools for younger patients are also likely to work in the elderly, even in those patients with mild or moderate cognitive impairment (Ferrell 1995; Bergh *et al.* 2000; Freedman and Peruvemba 2000).

5.3.3.1. Verbal Rating Scales (Figure 2, Table 2)

Verbal Descriptor Scale (VDS) is also called the Verbal Rating Scale (VRS) or the Graphic Rating Scale (GRS). These verbal rating tools are common and practical methods for assessing pain severity. Verbal Rating Scales include a series of word descriptions of pain intensity in ascending order. The pain intensity scores are based to the score of the McGill pain Questionnaire (MPQ) being the most frequently used form (Melzack 1975). VDS is a 6-grade scale ranging from 0 = none, 1 = mild, 2 = uncomfortable, 3 = distressing, 4 = horrible to 5 = excruciating pain. The Verbal Rating Scale (VRS) pain measurement tool is a nondimensional and nonlinear a five-point verbal categorical rating scale. Pain is assessed by asking the patient to select the descriptor (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain, 4 = unbearable pain) that best describes the intensity of the pain. A variation of the verbal rating scale includes a scale which has from 4 to 7 points, where the patient chooses the word that describes the pain “right now”.

The VRS is useful if the patient has a visual or motor impairment (Melzack 1975), whilst the VDS is a valid and reliable method for young people (Jensen *et al.* 1986) and evidence supports its use for chronic pain measurement in the elderly (Melzack 1975; Gagliese and Katz 2003). The VDS is reliable and has a high internal consistency as analyzed by Cronbach α (0.85-0.86), however test-retest reliability (r = 0.52-0.83) decreases in patients with cognitive impairment. The reliability of the VRS, on the other hand, has been validated in acute perioperative and postoperative pain, pain clinic, long-term care and community dwelling. VDS scales have also a strong positive correlation with other pain scales in many studies (Herr and Mobily 1993; Chibnall and Tait 2001; Herr and Garand 2001; Gagliese and Katz 2003; Gagliese *et al.* 2005). Verbal ratings scales (VRSs) provide a more sensitive tool for separating intensity and unpleasantness than nondescriptive scales (Duncan *et al.* 1989). In particular, the VRS is considered the most effective scale in elderly patients with cognitive impairment possibly due to retention of long-term verbal associations (Weiner *et al.* 1998; Weiner *et al.* 1999; Morrison and Siu 2000; Titler *et al.* 2003; Rakel and Herr 2004). A smaller number of the description words utilized for five point ranging, may be less demanding for older patients with cognitive impairment.

VRS scales have a limited number of possible responses, and the scales are noncontinuous. Therefore, the use of nonparametric statistical analysis is needed and it makes the VRS weaker than the VAS in research approaches (Ohnhaus and Adler 1975). The choice of words is important; the pain intensity scale of the MPQ appears to be the most widely used English language version (Taylor and Herr 2003). Moreover, the translation into other languages has been performed, as seen for Finnish (Ketovuori *et al.* 1984). The assessment of pain intensity by using verbal rating scales always demands language skills and patients need to communicate verbally.

5.3.3.2. Numerical Rating Scale

The Numeral Rating Scale (NRS) is a common and practical method for assessing pain severity. It is the most widely used pain rating scale in clinical practice (Weiner *et al.* 1998; Weiner *et al.* 1999; Morrison and Siu 2000; Herr *et al.* 2004; Gagliese *et al.* 2005). The NRS is an 11-point verbal pain scale, where patients are requested to quantify the intensity of their pain on a scale from zero to 10 (from 0 = no pain to 10 = worst pain imaginable). The variety of NRS scale ranges and anchors, including 0-5, 0-10, 0-20, and 0-100 scales, with 0 is no pain and 5 (10, 20, 100) is the most intensive pain. The NRS scale can also be used visually with both words and numbers along a vertical or horizontal line. Patients are asked to express a number that relates best to their pain intensity. There is evidence, which

supports the validity and reliability of the NRS in younger (Jensen *et al.* 1986; Breivik *et al.* 2008) and older patients (Gagliese and Katz 2003).

The numerical rating scale is widely used among patients in acute postoperative care, pain clinic, long-term care and community dwelling. The verbal version requires the ability of abstract thought and may be difficult for older patients. The reliability of the NRS is acceptable and it has a high internal consistency, with a Cronbach α range of 0.86 to 0.88 (Hadjistavropoulos *et al.* 2007). As for the VRS, the test-retest reliability of the numerical rating scale (r = 0.57-0.83) decreases in patients with cognitive impairment (Hadjistavropoulos *et al.* 2007). A smaller number of choices (0-5) may be useful and not too demanding for older patients. This 5-point NRS scale has been validated as already described for the VRS and the VAS (Jensen and Karoly 1992). It is advantageous that not only is the NRS straightforward and fast to use, but the pain intensity of patients can also be assessed without linear or visual representation, thus patients do not necessarily require visual skills. Nontheless, patients with cognitive impairment may have difficulty visualizing their pain in numerical terms and the numerical rating scale is not a suitable pain measurement tool for patients who are confused and disorientated (Hartrick *et al.* 2003).

5.3.3.3. Visual Analogue Scales (Figure 2, Table 2)

The Visual Analogue Scale (VAS) is a 10 cm line with endpoints labeled “no pain” and “worst possible pain”, where patients indicate the point on the line that best represents their current level of pain. The VAS maybe the most common pain measurement tool and it has become a standard tool in pain research and clinical practice (Scott and Huskisson 1976; Jensen *et al.* 1986). The VAS is reliable and well-validated and documented (Carlsson 1983; Chapman *et al.* 1985; Dalton and McNaull 1998). The internal consistency of the VAS is analyzed by Cronbach α 0.87-0.88 and the reliability of the test-retest is acceptable (r = 0.75-0.83) (Hadjistavropoulos *et al.* 2007). The VAS has a strong positive correlation with other pain intensity assessment tools (Herr and Garand 2001; Gagliese and Katz 2003; Ardery *et al.* 2003b; Taylor and Herr 2003; Breivik *et al.* 2008). However, many studies that have examined the reliability and validity of the VAS have either included in a limited number of patients or excluded the elderly (Gagliese and Katz 2003; Taylor and Herr 2003; Gagliese *et al.* 2005). Additionally, researchers have noticed that increased age was associated with a greater frequency of unreliable responses to the VAS (Benesh *et al.* 1997; Bergh *et al.* 2003).

The VAS is validated to measure both chronic and experimental pain (Price *et al.* 1983). Many studies have shown the linearity of the VAS scale over a large range of acute pain intensity (Myles *et al.* 1999; Myles and Urquhart 2005). Therefore, studies support that the changes in the VAS score express a relative change in the magnitude of pain intensity. The VAS is simple and easy to use among many different languages. The VAS has been compared to VRS (4-point) and NRS-11 in acute pain (Breivik *et al.* 2000) and it was found to be more sensitive than VRS (4-point), while the VAS and the NRS (11-point) were approximately equal (DeLoach *et al.* 1998).

Despite the fact that the VAS is a validated pain measurement tool, its administration requires health professional or nursing resources that may decrease compliance for its use. The VAS may be difficult to use immediately after general anaesthesia (Aubrun *et al.* 2003), and is a unidimensional assessment tool of pain intensity. It cannot represent all factors of pain perception widely enough. There are many circumstances in clinical practice, where the VAS has a high failure rate, such as in situations when patients visual, cognitive, or motor skills are impaired, when patients are moderately sedated or confused, and those in very severe pain with agitation (Benesh *et al.* 1997; Krulewitch *et al.* 2000; Bergh *et al.* 2001; Gagliese and Katz 2003; Closs *et al.* 2004; Herr *et al.* 2004; Gagliese *et al.* 2005; Pautex *et al.* 2005).

5.3.3.4. A 50 cm Red Wedge Scale (Figure 2, Table 2)

A 50 cm Red Wedge Scale (RWS) is a modified enlargement of the ordinary visual analogue scale. It is a 50 cm red coloured horizontal wedge (15 cm high at its end) which was developed initially for the assessment of pain immediately after surgery in patients recovering from general anesthesia (Tigerstedt and Tammisto 1988; Tarkkila and Saarnivaara 1999; Silvasti and Pitkänen 2001; Leino *et al.* 2011). A 50 cm Red Wedge Scale is simple and straightforward to use like the visual analogue scale (VAS). The advantage of the RWS is the large size. This scale is not widely used and it is not a validated ratio measure of chronic pain or clinical acute pain. This pain assessment tool is often used in research (Silvasti and Pitkänen 2001) and in clinical practice in Finland, but it is not well-known in other countries.

5.3.3.5. Facial Pain Scales (Figure 2, Table 2)

The Facial Pain Scale was first developed by Wong and Baker and it is recommended for patients aged over three years (Wong and Baker 1988). The scale was developed by asking children to draw their impression of facial expressions from no pain to

worst pain. A smiling face was most often drawn as the "no pain" anchor and the face with tears described the worst pain; although a neutral rather than happy no-pain anchor was employed by Bieri et al. (1990) associated with no tears at the upper anchor and less emotive expressions. A row of the six or seven different face pictures indicate the intensity of pain in this model, to which the numerical rating of pain intensity may be adapted under the different faces from 0-5 or to 0-10. The patient is asked to choose the face that best describes how they feel in this widely used pain measurement tool for children. The Facial Pain Scale approach is also practical for older adults in the clinical assessment of pain intensity (Bieri *et al.* 1990; Herr *et al.* 1998; Chibnall and Tait 2001; Taylor and Herr 2003; Kaasalainen and Crook 2003; Herr *et al.* 2004; Li *et al.* 2007; Li *et al.* 2009), in fact Bieri's modified version is also validated in adults (Bieri *et al.* 1990; Hicks *et al.* 2001).

The Facial Pain Scales are validated and reliable in children (Wong and Baker 1988; Bieri *et al.* 1990). The reliability of this pain scale has been measured by internal consistency Cronbach α (0.88-0.89) and by test-retest reliability (r = 0.44-0.94) (Kim and Buschmann 2006; Ware *et al.* 2006). The FPS is widely used and well-tested for both acute postoperative pain and chronic pain for both hospital and community dwelling patients, but its correlation with other pain intensity scales is quite weak. The FPS does not demand language and it is simple to use in clinical practice at all levels of heath care organization.

The use of facial pain scale figures may increase the possibility of confounding the results with emotional feelings such as depression that can change the degree of the pain intensity reported. Therefore, the differences of the faces may not be linear in terms of pain intensity and the facial scale may possess different degrees of sensitivity, although it is reported to be valid and reliable to measure pain (Kim and Buschmann 2006).

5.3.3.6. McGill Pain Questionnaire (Table 2)

The McGill Pain Questionnaire (MPQ) was developed in 1975 by Melzack for assessment of chronic pain. The MPQ is made up of 20 categories of adjectives that describe the qualities of pain. Patients choose those words or adjectives that the best describe their feelings and intesity of pain at that moment. The rank values of chosen words are summed to obtain total score. The MPQ includes three major measures; (1) Pain Rating Index (PRI), that is based on two types of numerical values that can be assigned to each word descriptor, (2) the number of the words chosen; and (3) the present pain intensity based on a 1-5 intensity scale, that is a modified single dimension five-point verbal descriptive rating scale (Melzack 1975). The MPQ is a multidimensional pain measurement tool. Evaluative, affective, and

sensory are the three dimension of the PRI's. The MPQ and the subclasses of the PRI have been found to be reliable and valid pain assessment tools. (Melzack 1987). The reliability of the MPQ has been found to vary from inadequate to adequate, whilst internal consistency has been measured by Cronbach α 0.41-0.98, and high test-retest reliability has been shown for total, sensory, affective, and average pain scores (Gagliese and Melzack 1997; Luggen 1998; Zalon 1999; Gloth *et al.* 2001; Grafton *et al.* 2005). The short-form MPQ (SF-MPQ) was modified by Melzack in 1987 (Melzack 1987) and includes sensory (sharp, shooting, etc.) and four affective (sickening, fearful, etc.) verbal descriptors. The patient rates the intensity of each descriptor on a scale from 0 to 3 (3 = severe). Three pain scores are calculated: the sensory, the affective and total pain index. The SF-MPQ includes visual analogue and verbal rating scales of pain intensity (Grafton *et al.* 2005; Melzack 2005). The MPQ has been translated into many languages; the Finnish version was translated from English (Ketovuori *et al.* 1984). The original MPQ is impractical in the clinical setting because the questionnaire is long and a nurse must pose the questions with the assessment of pain intensity taking at least fifteen minutes. Although the MPQ is a validated multilanguage tool for measuring chronic pain (Gagliese and Melzack 1997), it is an unsuitable pain measurement scale for routine clinical use to measure pain levels in the postoperative period. A newer preliminary version of SF-MPQ-2 has been developed to be a comprehensive measure of pain quality in both clinical research and clinical practice. The SF-MPQ-2 includes a single measure of the major sensory and affective symptoms of both neuropathic and non-neuropathic pain. It can be applied to epidemiology, natural history, pathophysiologic mechanisms and treatment response studies (Dworkin *et al.* 2009).

5.3.3.7. Behavioral Pain Assessment Tools and Scales

There are many circumstances when self-reporting of acute pain is not possible and the intensity of pain may be assessed using behavioral pain scores. In typical situations, patients are under the influence of residual sedatives or general anaesthetic agents, cannot respond verbally, and may have severe cognitive impairment or be intubated and sedated. Several attempts have been made to develop observational, clinically relevant tools for patients unable to self-report. Clinically relevant pain measurement tools may be categorized into those that are brief (compromising of 10 items or less) and those that are extended (compromising of more than 10 items) (Hadjistavropoulos *et al.* 2007). The most common method for determining the behavioral component of a patient's pain is by direct observation. The behavioral pain measurement scales of 10 items or less are the Discomfort Scale (DS-DAT) (Hurley *et al.* 1992), Checklist of Nonverbal Pain Indicators (CPNI) (Feldt 2000),

Pain Assessment in Advanced Dementia (PAINAD) (Warden *et al.* 2003), Pain Assessment in the Communicatively Impaired (PACI) (Kaasalainen and Crook 2003), Abbey Scale (Abbey *et al.* 2004), Non-communicating Patient's Pain Assessment Instrument (NOP-PAIN) (Snow *et al.* 2004), the Doloplus-2 (Wary and Doloplus 1999), and the Pain Assessment Tool in Confused Older Adults (PAT-COA) (Decker and Perry 2003). Despite the numerous behavioral pain scales, many studies have shown that the majority of these measures have unsatisfactory or unreported internal consistency, introducing uncertainty about whether items measure the same construct (Feldt 2000; Decker and Perry 2003; Warden *et al.* 2003).

Numerous behavioral pain measures of more than 10 items have been developed to assess pain among patients with dementia. These tools are Amy's Guide (Galloway and Turner 1999), The Pain Assessment in demented Elderly Scale (PADE) (Simons and Malabar 1995), and the Pain Assessment Checklist for the Seniors with Limited Ability to Communicate (PACSLAC) (Fuchs-Lacelle and Hadjistavropoulos 2004).

The relationship between behavioral tools and the pain intensity rating has not been declared. However, behavioral scales may be the only possible assessment tools for severely demented patients, where the behavioral pain scales may not be suitable for general postoperative pain assessment (Wary and Doloplus 1999; Morrison and Siu 2000; Fuchs-Lacelle and Hadjistavropoulos 2004).

5.3.3.8. Problems in assessing pain in dementia

Dementia causes serious and unique barriers to pain assessment. It can be generally characterized by memory loss, personality changes, and loss of many functions such as abstract thinking, language skills and judgement. The impairment level is often categorized by measurement of the Mini Mental State Examination (MMSE) score (Folstein *et al.* 1975). The impact of dementia on pain processing varies in direction and quality, depending on the type of pain, neuropathology and stage of dementia. Self-reporting is considered to be the standard of pain assessment and these scales require the capacity to understand the task and to communicate about pain experienced. Ageing has been associated with difficulties in grasping abstract concepts that creates difficulty in using scales requiring cognitive skills (Gagliese and Melzack 1997). Accordingly, recent studies describe the insufficient reliability and validity of self-report scales in patients with dementia (Fisher *et al.* 2002; Pautex *et al.* 2006), suggesting that behavioral and observational assessment scales are required (AGS Panel on Persistent Pain in Older Persons 2002). However, typical pain behaviors may be absent or difficult to interpret among non-verbal older patients with severe dementia (Fuchs-Lacelle *et al.* 2008).

5.4. PHYSIOLOGICAL CHANGES IN THE ELDERLY

Physiological changes in the elderly may affect in the management of pain. There are age-related differences in the perception of, and response to, pain (Gibson and Helme 2001). The response to mild pain is often reduced in many older patients. On the other hand, older people may be more sensitive to severe pain. The reasons for these age-related changes are still unclear (Gibson and Helme 2001).

5.4.1. PHYSIOLOGICAL CHANGES IN CARDIOVASCULAR FUNCTION IN ELDERLY PEOPLE

Cardiovascular disease affects approximately 50 to 65% of elderly patients; physiological changes include a decrease in cardiac index of 1% per year after the age of 30 years (Lund-Johansen 1988; Tumer *et al.* 1992). Furthermore, hypertension can reduce cardiac function and the subsequent lower cardiac output induces a decrease in hepatic blood flow. This in turn impacts on the clearance of opiods that have relatively high extraction ratios across the liver (Upton and Huang 1993; Aubrun *et al.* 2002; Macintyre 2005). Furthermore, reduced cardiac output can lead to higher peak arterial opioid concentrations after intravenous administration, as a function of dilution, cardiac output, and the kinetics of the first pass of the drug through the lungs. Therefore, the strategy for administration of intravenous opioids therefore is to reduce the initial dose and to use slower injection rate in elderly (Upton 1996; Weiss *et al.* 1996).

5.4.2. PHYSIOLOGICAL CHANGES OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM IN ELDERLY PATIENTS

The elderly have a reduction in cerebral blood flow, and an increased responsiveness to CNS-active medications (Tumer *et al.* 1992). Sub-cortical and cortical atrophy decreases receptor sites, receptor affinity and the synthesis of the neurotransmitters acetylcholine, dopamine, GABA and noradrenaline. Neuronal loss is greatest in the neocortex and hippocampus (mainly in region of locus ceruleus and substantia nigra) and may affect pain. G-proteins, a secondary mediator of the action of many receptors including opioid receptors, have decreased coupling. There is reduced catalytic activity of adenylate cyclase which is a secondary mediator of pain. Many of these changes provide reason for drug-induced delirium and reduced drug tolerance in the elderly (Tumer *et al.* 1992; Davis and Srivastava 2003).

Nerve conduction is slowed in the aged. There is an age-related decrease in the capacity or speed of processing of nociceptive stimuli. Furthermore, C and Aδ fiber

function decreases with age. A corresponding degeneration of electrical conduction occurs along motor pathways. Peripheral motor nerve conduction decreases by about 0.15 m/s/year (Harkins *et al.* 1994). There are structural, biochemical, and functional changes in the peripheral nervous system with age, together with increased neuronal damage and deterioration. There is a reduction in the content and turnover of neurotransmitter systems, that is known to be involved with nociception (Clark *et al.* 2004). A slowing in peripheral nerve conduction velocity and similar changes in the central nervous system may be the cause of the change in pain sensitivity. Many studies have shown that the age-related pain threshold changes, although some results of the studies were in contradiction with each other. Furthermore, many studies have been methodologically weak (Harkins *et al.* 1994; Gibson and Helme 2001; Gagliese and Katz 2003). Overall, most studies have documented that the elderly demonstrate an increase in the pain perception threshold.

5.5. CLINICAL PHARMACOLOGY IN THE ELDERLY

Age-related physiological changes affect different organ systems. Therefore, important pharmacodynamic and pharmacokinetic changes occur with advancing age. Moreover, the individual variability in the physiological responses increases with age. Ageing is not a single matter but a collective term representing the sum of cumulative local effects at molecular, cellular and tissue level. The most logical change is the time-related loss of organs functional units like as nephrons in kidney, alveolis in lungs and neurones in brains. This reduction of functional reserve is associated with a decrease in viability and an increase in vulnerability (Mangoni and Jackson 2004).

5.5.1. PHARMACOKINETIC CHANGES IN THE ELDERLY

5.5.1.1. Absorption

The oral absorption of drugs remains stable in elderly patients with an intact gastric mucosa, despite increased gastric pH and decreased gastrointestinal blood flow. However, absorption may be altered by nutritional deficiencies, partial gastrectomy, and drug interactions with laxatives, antacids, and agents that decrease gastric emptying. In general, the rate and extent of drug absorption from the gastrointestinal tract remains unchanged (Cusack *et al.* 1980). Using paracetamol as a marker, it has been shown that the rate of gastric emptying and absorption of orally administered drugs does not change substantially with age (Gainsborough *et al.* 1993). Aging is associated with a reduction in first-pass metabolism because of the reduction in liver blood flow. Decreased hepatic clearance and its causes correspondingly increases

bioavailability leading to higher blood concentrations of some orally administered drugs (Mangoni and Jackson 2004).

5.5.1.2. Distribution

The volume of distribution (V_D) is not an actual physiological measurement but it is pharmacokinetic measurement defined as the amount of drug in the body divided by the concentration of drug in the blood or plasma per kilogram of body weight. Increasing age is associated with increased body fat and reduction in the total body water. Drugs that distribute into muscle or into body water will achieve a high initial plasma concentration after administration as a decrease in their V_D.

Water-soluble drugs are distributed less effectively in elderly patients with decreased muscle mass and body water. The smaller volume of distribution causes higher serum levels of water soluble drugs in elderly patients. The increase in fatty tissue in the elderly increases the V_D of lipophilic drugs because fat acts as a depot of these agents which include diazepam and haloperidol (Bressler and Bahl 2003).

The binding of drugs to plasma proteins usually decreases with aging. Nonetheless, no changes are observed in the binding of α1-acid glycoprotein to basic drugs. Most drugs are acidic and thus are instead bound by serum albumin. Total serum albumin and its drug binding capacity is decreased by about 12% in elderly patients. Given that free drug concentrations determine the pharmacological effect, because bound drug cannot bind to target tissues, the total plasma levels in the elderly are thus likely to be decreased. This effect may also accentuated by the observation that many diseases in the elderly can depress albumin levels; including chronic diseases that require drug therapy, such as heart failure, renal disease, rheumatoid arthritis, hepatic cirrhosis, and some malignancies. Decreased protein binding causes to the need to adjust doses for elderly patients. Renal disease is documented to decreased plasma albumin and it may lead to acidosis, both of which will decrease drug binding (Bressler and Bahl 2003).

5.5.1.3. Drug elimination

Clearance and half-life

Two pharmacological concepts, clearance and half-life, are important to understand therapeutic and adverse drug reactions in the elderly. The effects of the drugs relate to the level of drug concentration in the blood, thus the processes that eliminate drugs from the blood become significant considerations (Bressler and Bahl 2003). Clearance is the measure of fractional loss of the drug per unit time, therefore the amount of blood volume completely cleared of drug per unit time. It represents the

efficiency of drug extraction from blood. Clearance does not direcly indicate how much drug is being removed, on the contrary, it suggests the volume of plasma that would need to be freed of drug to account for the elimination of the drug (Bressler and Bahl 2003).

The half-life of a drug is the time which it takes for the drug concentration in plasma to decrease by 50% after drug distribution. The elimination half-life of drugs increases with age. This may be caused by decreases in drug clearance.

Metabolism and changes in hepatic function

Aging is associated with a reduction in hepatic function. A 1% decline in cardiac output per year after the age of 30 induces a 0.5 to 1% reduction in hepatic blood flow with a decrease in liver clearance (Aubrun 2005). The activity of hepatic microsomal enzymes declines slowly with age, while the distribution volume of lipid-soluble drugs increases, because of the proportion of body fat increases with ageing.

Elimination and changes in renal function

The main reason for changes in drug action in the elderly, is that drug elimination is less efficient in old people. Therefore, drugs produce greater and more prolonged effects at the extremes of life. Renal function decreases with age (Hansen *et al.* 1970; Papper 1973). Total renal blood flow decreases 10% per decade in adults and the glomerular filtration rate (GRF) reduces 1 to 1.5% per year after the second decade. Also the aging influences tubular secretion, tubular reabsorption, and renal metabolism. Creatinine clearance gives the most reliable measurement of GFR. The measurement of serum creatinine remains often within normal range despite of impaired GRF. The marked reduction of the proportion of the skeletal muscle to total body mass causes a small creatinine load. Creatinine values are based on catabolism of muscles, and are not a sensitive measure of renal function in the elderly. A 50 to 70% decrease in the GRF induces only a moderate increase creatinine concentration. The drugs that are eliminated substantially by renal excretion should be given in reduced doses and less frequently to older patients in order to avoid accumulation and untoward pharmacologic effects.

5.5.2. PHARMACODYNAMIC CHANGES IN THE ELDERLY

Significant pharmacodynamic changes occur in the elderly, which tend to indefinitely increase drug sensitivity. The effect of age on drug sensitivities varies with the drug studied and the response measured, thus generalizations are difficult to make. Studies of drug sensitivity require measurement of concentrations of drug in plasma as differences in pharmacokinetics with increasing age may increase or decrease differences in response to the drug (Mangoni and Jackson 2004; Bowie and

Slattum 2007). Only a few studies of pharmacokinetic-pharmacodynamic relationships for opioids have been reported, most of which have used a measure of effect other than clinical pain relief. The effects of fentanyl, alfentanil and remifentanil were investigated on the electroencephalogram (EEG) and it was concluded that the kinetics of these opioids were not influenced by age. However, the sensitivity of the brain to opioids was increased by 50 percent (Scott and Stanski 1987a ; Minto *et al.* 1997). Aging is also associated with increased sensitivity to the central nervous system effects of benzodiazepines, although the exact mechanisms for this are unknown (Kruse 1990).

5.5.2.1. Sensitivity

The changes in altered responsiveness to drugs may occur at the level of receptor (biochemical, structural, translational), tissue or organ, and homeostasis. Aging is associated with lower receptor density or changed characteristics, such as the sensitivity to catecholamines. The number of receptors can also be altered rapidly in terms of up or down regulation by both physiological and pathological processes, as well as by drugs (Tumer *et al.* 1992).

5.6. PAIN MANAGEMENT IN THE ELDERLY

The main goal of pain management is pain reduction associated with improved function, reflected in the activities of daily living, sleep, and well-being after surgical operations or chronic painful diseases. Management strategies for acute and chronic pain in the elderly comprise combinations of treatments. These may be relatively common using opioid and non-opioid analgesics, or more complicated approaches using combinations of regional or local blocks with opioids, non-opioid analgesics, or both. Pain treatment strategies do not differ between middle-aged and elderly patients in normal clinical practice, although it is well-known that aging is associated with decreased organ function, varied responses to drugs, and increased incidence of multi-system disease.

5.6.1. OPIOIDS IN THE PAIN MANAGEMENT IN THE ELDERLY

Opioids are a mainstay for treating acute moderate and severe postoperative pain in the elderly. Many studies have shown that the elderly require less opioid for management of acute pain than younger patients (Macintyre and Jarvis 1996; Coulbault *et al.* 2006). Safe and effective opioid analgesia requires age-related dosage sched-

ules, careful titration of effects, intensive assessment of pain, the use of a suitable drug and route, in addition to awareness of problems with metabolites of opioids. Age appears to be a better determinant of the dose of an opioid than the patients weight (Gagliese *et al.* 2000; Aubrun *et al.* 2003; Aubrun and French Society of Anesthesia and Resuscitation 2009). On the other hand, the decrease in opioid requirement is not associated with reports of increased pain. The use of opioids is becoming more acceptable for the management of chronic pain that impairs daily function and quality of life in elderly patients (AGS Panel on Persistent Pain in Older Persons 2002; Reid *et al.* 2010).

5.7. PAIN MANAGEMENT DURING CARDIAC ANESTHESIA

5.7.1. FENTANYL IN CARDIAC SURGERY ANAESTHESIA

Fentanyl, (N-(1-phenethyl-4-piperidyl) propionanilide), is a μ-receptor agonist and a synthetic opioid with high potency and lipophilicity. It is structurally related to meperidine. The widespread use of fentanyl began between the years 1975 and 1981. It is a potent intraoperative analgesic agent with relatively few adverse effects, haemodynamics remains stable when fentanyl is used to induce and maintain anesthesia in critically ill patients. An elimination half-life of fentanyl is 3.5 hours and the time to peak effect is about 4 minutes. Fentanyl is metabolized in the liver to yield metabolites (Hudson *et al.* 2002), the pharmacological activity of which is unknown; however they appear to be clinically insignificant. Less than 10% of fentanyl is removed unchanged by the kidney (McClain and Hug 1980; Shafer *et al.* 1990).

High-dose (50-150 μg kg^{-1}) fentanyl was used widely for cardiac anaesthesia in the late 1970s because of its superior haemodynamic profile, however this approach was abandoned due to dose dependent bradycardia, chest wall rigidity and the need for prolonged mechanical ventilation. Nontheless, intermediate-dose (10-15 μg kg^{-1}) fentanyl remains the mainstay of balanced general anaesthesia in many centers (Ahonen *et al.* 2000; Hudson *et al.* 2003; Silbert *et al.* 2006). After intravenous administration, fentanyl distributes rapidly from plasma to vascular tissue, muscle and fat (McClain and Hug 1980). Removal of fentanyl from muscle and fat is slower than uptake and after continuous long-term administration fentanyl accumulates in the body (Stanski *et al.* 1978).

Fentanyl has been administered via intramuscular, intravenous (bolus, injection, infusion, patient-controlled analgesia), neuraxial and inhalational routes. Recently, new administration routes have also been developed, including a trans-dermal patch for use in chronic pain (Clark *et al.* 2004). Opioid related side effects such as respiratory depression, sedation and itching are to be expected, thus fentanyl

should be used only when ventilation is controlled or it can be monitored. Fentanyl is still widely used as an anesthetic agent in adults undergoing cardiac surgery for whom fast postoperative recovery and earlier tracheal extubation have become an important goal in their anaesthetic management. Additionally, fentanyl is used as a postoperative analgesic, typically administered either intermittently (0.5-2 μg/kg) or as an infusion (0.5-2 μg/kg/h). Fentanyl has an excellent haemodynamic stability and limited allergic potential (Howie *et al.* 2001; Myles *et al.* 2002; Payen *et al.* 2007).

5.8. PAIN MANAGEMENT IN THE INTENSIVE CARE UNIT AFTER CARDIAC SURGERY PATIENTS

Pain intensity after cardiac surgery is moderate or severe and often under-treated. Opioids, paracetamol, and more recently anticonvulsants are used as an analgesic regimen after cardiac surgery in the intensive care (Diby et al. 2008; Layzell 2008; Menda et al. 2010). The incidence of chronic pain after cardiac surgery varies from 21 to 55% (Macintyre and Russell 2003; Lahtinen et al. 2006; Macintyre et al. 2006). Risk factors for chronic pain are younger age (< 60 years), longer duration of surgery (> 2 hours), depression, cultural background, female gender and low education (Kehlet et al. 2006; Sommer et al. 2008; Tan et al. 2008).

5.8.1. OXYCODONE IN POSTOPERATIVE PAIN MANAGEMENT AFTER CARDIAC SURGERY

Oxycodone has been widely used for the relief of moderate and severe acute postoperative pain and cancer pain in Finland since the 1960s (Kalso 2005b). It can be administered via a variety of routes including oral or rectal, intramuscular, intravenous, or subcutaneous injection. Oxycodone (14-hydroxy-7,8-dihydrocodeinone) is a semisynthetic opioid analgesic and an agonist of μ-opioid receptors. It also binds to κ-opioid and δ-opioid receptors with a lower affinity than to μ-receptors. The volume of distribution of oxycodone is about 2-3 L/kg and its elimination half-life is about 2.3-2.6 hours after i.v. administration. The maximum plasma concentration of oxycodone is achieved within 25 min. after i.v. administration (Pöyhiä *et al.*1991). Intravenous oxycodone was associated with a rapid pain relief in between five to eight minutes. Alternatively, oxycodone is well absorbed after orally dosing, with more bioavailability than morphine when it is given orally (Pöyhiä *et al.* 1992). Oxycodone has been found to be more potent than morphine for visceral pain relief but not for sedation after laparoscopic hysterectomy (Kalso *et al.* 1991; Lenz *et al.* 2009). Oxycodone is available as single agent, in controlled release (CR) and im-

mediate release (IR) formulations. The elimination half life is about 3 hours after (IR) oxycodone and about 8 hours after (CR) oxycodone, however the maximum plasma concentrations of oxycodone are achieved after 1.3 h after IR and 2.6 h after CR oxycodone (Mandema JW *et al.* 1990).

Oxycodone is mainly metabolized in the liver through the cytochrome P450 enzyme system to noroxycodone via a major pathway (CYP3A) and to oxymorphone via a minor pathway (CYP2D6). Noroxycodone is a weak opioid agonist and it has a little antinociceptive activity. This active metabolite increases the potential for interractions with other drugs metabolized by the CYP3A4 pathway. Oxymorphone metabolite forms only small amounts after oxycodone administration. It has greater μ-receptor binding affinity than oxycodone. Noroxymorphone is a second oxidative metabolite producted by O-demethylation of noroxycodone. However, the analgesic effect of noroxycodone is not yet clearly known (Lalovic *et al.* 2004).

Oxycodone metabolism can differ in population according to age, sex, and ethinicity. The plasma concentrations of oxycodone might be higher in elderly and in female compared to younger and male subjects (Kaiko RF *et al* 1996). The ethinicity and genetic background have impact to the metabolism of oxycodone to oxymorphone. The minor part (1-7%) of Caucasians are ultra-rapid CYP2D6 metabolizer and the small part (5-10%) of people are poor metabolizers due to decreased CYP2D6 activity. Therefore, the ultra-rapid CYP2D6 metabolizers may reduce analgesic response. In contrast, the poor metabolizers may increase analgesic and adverse effects of oxycodone (Kalso E 2005b).

Oxycodone and its metabolites are excreted and eliminated via the kidney. About 8 to 14% of oxycodone doses are excreted as free oxycodone, about 50% as conjugated oxycodone, 0% as a free oxymorphone, and 14% as conjugated oxymorphone, while free and conjugated noroxycodone have been demonstrated. Therefore, oxycodone elimination is decreased with renal insufficiency due to a large volume of distribution and reduced clearance (Pöyhiä *et al.* 1993; Kirvelä M *et al.* 1996). Parenteral oxycodone is used as a primary opioid for early postoperative pain after cardiac surgery in Finland (Lahtinen *et al.* 2002; Lahtinen *et al.* 2004). Typically the administration of oral oxycodone is started on the first postoperative day and patients usually routinely receive additional analgesia with paracetamol after cardiac surgery.

5.8.2. SIDE EFFECTS OF OPIOIDS IN THE ELDERLY

The potential for side effects is greater in the elderly because of changed distribution and excretion of drugs. Also, impairment of renal and hepatic function is common in the elderly. Renal dysfunction increases the half life of active drug and metabolites, therefore the risk of opioid side effects increases in the elderly (Bressler and Bahl

2003; Bowie and Slattum 2007). The most commonly reported adverse effects in the elderly are constipation, nausea, dizziness, somnolence and respiratory depression (Roth *et al.* 2000). The risk of respiratory depression and over sedation are known to be greater in the elderly than in younger adults. The best and the earliest clinical symptom of respiratory depression appears to be sedation (Vila et al. 2005). Sedation should be monitored in elderly patients given opioids by using a sedation score, such as the doses of opioids should be reduced in elderly. The level of sedation must be followed intensively during pain management (Bressler and Bahl 2003). Postoperative nausea, vomiting and constipation are common side effects that are more likely for female patients, non-smokers, the aged, those using opioids, and those suffering anxiety (Roth *et al.* 2000).

5.9. POSTOPERATIVE CONFUSION, COGNITIVE DYSFUNCTION AND DELIRIUM AFTER CARDIAC SURGERY

Patients who undergo cardiac surgery have a higher risk of developing postoperative confusion and delirium. Known risk factors for confusion and delirium are advanced age, preexisting cognitive impairment, medications, administration of intraoperative and postoperative anesthetic and analgesic including opioids. Delirium or acute postoperative confusion is a temporary mental disorder, which appears frequently among hospitalized elderly patients. The incidence and prevalence of delirium vary widely among different study populations. Generally, delirium has been related to the long term cognitive and functional recovery, prolonged ICU and hospital stay and nursing home placement (Inouye *et al.* 1999; Koster *et al.* 2008).

5.10. PARACETAMOL

Paracetamol is widely used as an analgesic agent for postoperative pain or chronic pain in combination with opioids. It is well established as an effective and well tolerated drug for the management of mild and moderate pain. Paracetamol is recommended as a first line analgesic for the treatment of pain and fever in adults and children and is often used as a routine background analgesic in combination with opioids. Paracetamol has oral, rectal, and intravenous formulations. The intravenous route is especially advantageous after surgery, when it is not possible to use oral or rectal routes (Holmér Pettersson *et al.* 2006).

Despite many clinical studies and the widespread clinical use of paracetamol, the mechanism of paracetamol's analgesic action is not fully understood. Paracetamol has an influence on both the central and peripheral components of the pain pathway (Bonnefont *et al.* 2003). It has been shown to contribute to the direct inhibition of

the *N*-methyl-*D*-aspartate receptor, which stimulates the substance P-dependent synthesis of nitric oxide; it also inhibits prostaglandin synthesis. Recent findings suggest that the mechanism of paracetamol analgesic action is associated with the serotoninergic system (Pickering *et al.* 2006). Paracetamol is commonly administered to elderly patients, and the clinical pharmacological properties of paracetamol are well-known in the elderly. Liukas et al. have studied the pharmacokinetics of intravenous paracetamol in elderly patients, finding that a higher age and being female were associated with a higher exposure of paracetamol (Liukas *et al.* 2011).

5.10.1. PARACETAMOL IN POSTOPERATIVE PAIN MANAGEMENT AFTER CARDIAC SURGERY

Intravenous paracetamol is used for early postoperative pain management when patients are intubated and not able to take an oral analgesic. Oral paracetamol is used as soon as possible after extubation. The first initial intravenous prodrug formulation of paracetamol (propacetamol) was used for adults as an alternative to NSAIDs in the preoperative and postoperative period. Propacetamol reduced morphine consumption by 22 to 46% in patients undergoing major orthopaedic surgery (Remy *et al.* 2005). Alternatively, a new intravenous paracetamol, Perfalgan ®, is very well tolerated in many clinical studies (Grundmann *et al.* 2006; Kemppainen *et al.* 2006; Atef and Fawaz 2008). Intravenous paracetamol is considered to be a safe drug after cardiac surgery as emergency adverse reactions occur extremely rarely (Gregoire *et al.* 2007). Intravenous paracetamol is not associated with gastrointestinal lesion ulceration, renal dysfunction, or bleeding caused by platelet inhibition. Intravenous paracetamol in combination with tramadol provides effective pain control after cardiac surgery (Cattabriga *et al.* 2007). Holmér Pettersson et al. have studied plasma concentration following repeated rectal or intravenous administration of paracetamol after heart surgery. An initial intravenous dose of paracetamol has been found to be a valid method for reaching an early effective plasma concentration (Holmér Pettersson *et al.* 2006).

5.10.2. COMBINATION OF OXYCODONE AND PARACETAMOL IN THE POSTOPERATIVE PAIN MANAGEMENT

Pain is caused by multiple mechanisms of action. Consequently, the use of combination analgesic therapy has an influence on several targets and processes in pain reduction. The combination of oxycodone and paracetamol, for example, may decrease dose-related side effects as lower doses of the component drugs are used in chronic non-malignant pain and acute postoperative pain (Lahtinen *et al.* 2002;

Remy *et al.* 2005; Barkin 2001). Opioids are a cornerstone of postoperative pain management after sternotomy despite the numerous unwanted side effects. Nausea and vomiting, drowsiness, respiratory depression, constipation and bladder dysfunction are often observed during opioid analgesia. Multimodal or balanced analgesia, that is the combination of non-opioid analgesic to opioid, have been proposed to decrease opioid consumption, as seen for morphine or oxycodone, and to improve postoperative pain management after surgery (Kehlet and Dahl 1993). NSAIDs have numerous disadvantages such as bleeding and renal complications. Regional neuraxial anaesthesia is controversial due to the anticoagulation triggered in cardiac surgical patients. Therefore, intravenous or oral paracetamol combined with oxycodone is routine regimen in our clinical practice. Paracetamol is considered to be quite safe, even though it is not so highly effective, but in comparison, adverse effects of opioids have not been shown to decrease upon dosage reduction in the postoperative period (Remy *et al.* 2005). A meta-analysis was published by Marret et al, where the benefits of combining NSAIDs and morphine to decrease opioid-related side effects such as PONV and sedation but not pruritus, urinary retention, or respiratory depression (Marret *et al.* 2005). However, the combination of oxycodone and paracetamol may decrease the dose-related side effects of opioids as lower doses of opioid are used in postoperative pain (Barkin 2001).

5.11. GABAPENTINOIDS

Gabapentin and the related compound, pregabalin, are efficacious drugs in the treatment of different disorders including epilepsy, acute and chronic pain (Dallocchio *et al.* 2000; Dworkin *et al.* 2003; Frampton and Scott 2004; Rorarius *et al.* 2004; Tiippana *et al.* 2007), and anxiety (Rickels *et al.* 2005). Pregabalin has been shown to effectively decrease cancer-associated neuropathic pain, diabethic neuropathy, post-herpetic neuralgia, reflex sympathetic dystrophy and trigeminal neuralgia (Dallocchio *et al.* 2000; Eckhardt *et al.* 2000).

5.11.1. PREGABALIN -MECHANISM OF ACTION, PHARMACOKINETICS AND SIDE EFFECTS

Pregabalin is a specific ligand of the alpha-2-delta type 1 and 2 subunits of voltage-gated calcium channels, thus decreases depolarization-induced calcium influx at nerve terminals (Taylor *et al.* 1993). Pregabalin also decreases calsium inward currents, and reduces glutamate, norepinephrine and substance P content in the brain (Dooley *et al.* 2000). Pregabalin is structurally related to GAB_A (gamma-aminobutyric acid), it does not interact with either $GABA_A$ or $GABA_B$ receptors and

is not an inhibitor of GAB_A uptake or degradation (Ben-Menachem 2004; Bialer *et al.* 2004; Bialer 2005).

Pregabalin is fast and extensively absorbed after oral dosing; a maximal plasma concentration is achieved 1 hour after single or multiple doses. The steady state of the drug is reached within 24-48 h after repeated administration (Ben-Menachem 2004). Pregabalin can be started at an effective dose of 150 mg/day. Maximal plasma pregabalin concentrations (C max) and total exposures (AUC) are proportional to dose after either single or repeated dosing. The oral bioavailability of pregabalin is high at over 90% and is independent of the dose and the drug undergoes minimal metabolism (< 2%). Therefore, 98% of the drug is secreted as unchanged drug by renal excretion. The half-life of pregabalin is 5.8-6.3 hours and it is not bound to plasma proteins (Bialer *et al.* 2004). Furthermore, pregabalin should have a very low potential for drug-drug interactions because it is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. While pregabalin is neither metabolized nor bound to plasma proteins, it is not expected to trigger drug-drug interactions via these mechanisms in clinical practice. The lack of remarkable drug interactions is a benefit as pregabalin can be safely used with other durgs. It should be suitable for elderly patients who may receive other medications (Ben-Menachem 2004).

Pregabalin is well tolerated and associated with dose-dependent adverse events. Dizziness and somnolence are the most frequently reported side effects. Also dry mouth, peripheral edema, blurred vision, weight gain and abnormal thinking have been reported pregabalin treated patients (Gajraj 2007).

5.11.2. PREGABALIN FOR ACUTE PAIN IN ADULTS

Gabapentinoids, gabapentin or pregabalin, may be very useful analgesics in multimodal analgesia for the management of acute postoperative pain (Rorarius *et al.* 2004). Pregabalin have shown to have a significant opioid sparing and analgesic effect in a number of surgical settings postoperatively (Fassoulaki *et al.* 2006; Tiippana *et al.* 2007; Agarwal *et al.* 2008; Freedman and O'Hara 2008; Jokela *et al.* 2008a; Jokela *et al.* 2008b; Mathiesen *et al.* 2009; Gilron *et al.* 2009; Burke and Shorten 2010; Buvanendran *et al.* 2010;). In many studies, pregabalin has been administered only as a single dose before surgery. There are also many studies, in which gabapentinoids were not found to be beneficial in the management of acute postoperative pain (Agarwal *et al.* 2008; Jokela *et al.* 2008b; Mathiesen *et al.* 2009). Dauri et al. have published a systematic-narrative review of the clinical studies, where gabapentin and pregabalin have been used for acute postoperative pain management: they concluded that both, gabapentin and pregabalin reduced pain and opioid consumption after surgery on confront with placebo. However,

more randomised clinical trials (RCTs) are needed to compare gabapentinoids with other postoperative regimens and to study for a longer postoperative period (Dauri *et al.* 2009). The optimal dose and duration of the postoperative treatment with gabapentioids are not clear.

5.11.3. PREGABALIN FOR ACUTE PAIN IN ADULTS AFTER CARDIAC SURGERY

Although gabapentinoids have been studied widely in clinical analgesia studies (Tiippana *et al.* 2007; Dauri *et al.* 2009), there is very little information on their use after cardiac surgery and in elderly patients. The effect of gabapentinoids on postoperative pain after cardiac surgery and in the elderly is still unclear. A single dose of gabapentin was reported to reduce morphine consumption and postoperative pain in middle-aged patients after cardiac surgery (Menda *et al.* 2010). However in contrast, another recent clinical study reported, that preoperative gabapentin followed by postoperative dosing for two days did not affect postoperative pain, sleep, or opioid consumption after cardiac surgery (Rapchuk *et al.* 2010). Parlow et al. have shown that plasma gabapentin concentration was unaltered during CPB following preoperative administration (Parlow *et al.* 2010).

6. AIMS OF THE STUDY

The main purpose of the present work was to investigate the measurement and the management of pain in patients suffering various stages of cognitive impairment, patients in long term hospital care, and cognitively normal elderly Finnish patients after cardiac surgery.

The specific aims were:

1. To evaluate the correlation between pain intensity, daily activities, cognitive state, depression and their interrelationship in home-dwelling elderly people with chronic pain (I).
2. To evaluate the usefulness of four simple pain scales in cognitively impaired patients in long term hospital care and cognitively normal patients (II-III).
3. To investigate the association of opioid effects and plasma concentrations of fentanyl and oxycodone between elderly and middle-aged patients after cardiac surgery (IV).
4. To study the influence of pregabalin on consumption of oxycodone, postoperative confusion and chronic pain after cardiac surgery in elderly patients (V).

7. PATIENTS AND METHODS

7.1. PATIENTS

This study was performed in Oulunkylä Rehabilitation Hospital in Helsinki (study I), in the department of geriatrics in Katriina Hospital, Vantaa (study II) and in the departments of Anaesthesiology and Intensive Care Medicine and in the departments of Cardiothoracic Surgery (studies III-V), Helsinki University Central Hospital, between February 2002 and August 2009. The study protocol of study II was approved by the local Ethics committee of Katriina Hospital in Vantaa. The protocols for studies I and III-V were approved by the Ethics Committees of Helsinki University Central Hospital. All patients were informed about the purpose of the study before participating in the study. The patients or their relatives gave a written informed consent. The total number of patients was 366 (178 females and 188 males). The mean age of patients was 77 years (SD ± 8; figure 1). The youngest patient of these studies was 32 years old and the oldest patient was 96 years old. The oldest cardiac surgery patient was 91 years. Exactly 60 patients suffered chronic pain and 300 patients suffered acute pain. Twenty orthopaedic patients and 280 cardiac surgery patients participated these studies I-V (Table 2). Seven patients (2%) refused to participate in the studies.

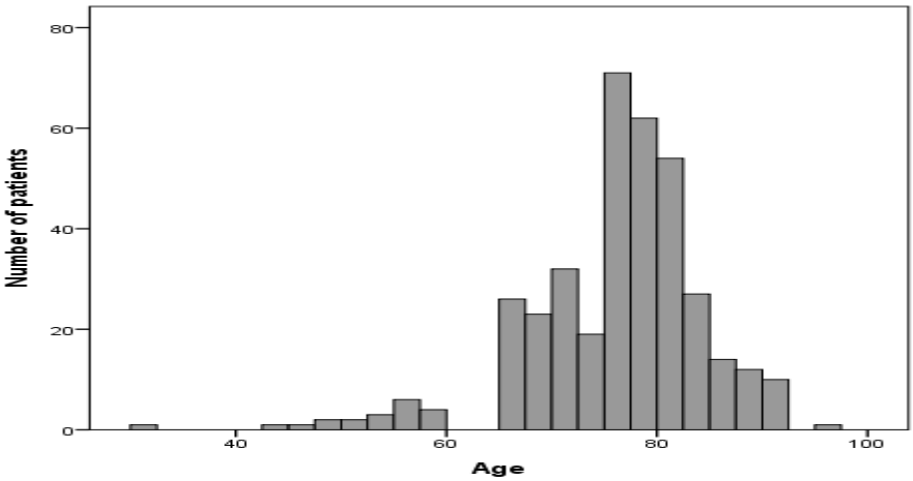


Figure 1. Histogram of patients age in studies I-V.

Study I-II

Study I was performed on war veterans participating in 2-week government-supported rehabilitation programs for various disabilities and pain. The subjects were home-dwelling citizens and during the program they stayed in a patient hotel attached to the institution, Oulunkylä Rehabilitation Hospital, Helsinki. The subjects for this pain study were selected from those who had reported moderate or strong pain as part of their need for rehabilitation in the admission charts.

Patients were recruited from the geriatric department (201 beds) of the primary health care hospital Katriina (Vantaa City, Finland). Forty-five long-term care patients (76-95 years, 5 males, 40 females) were selected based on signs or symptoms that indicated the presence of pain.

Study III-V

Exactly 160 Finnish-speaking patients, aged over 65 years, were studied after cardiac surgery in study III. Patients older than 65 years undergoing elective coronary by-pass (CABG) or valvular repair were allocated by turns into two groups, the red wedge scale (RWS n = 80) or the facial pain scale (FPS n = 80) group at random according to the operation number of the clinical computer list one day before the preoperative visit. The exclusion criteria for this study were dementia and cognitive impairment. The patients were autonomous perioperatively, non-hospitalized and able to carry on their daily routines. They were scheduled to undergo elective CABG with cardiopulmonary bypass (CPB) or with a beating heart (off-pump) technique or valve repair surgery with CPB. A standard median sternotomy was used in all patients and postoperative drainage tubes were inserted according to accepted clinical practice.

Exactly 30 patients aged over 75 years and 20 patients under 60 years, scheduled for elective CABG with CPB or for valve surgery with CPB, were enrolled in study IV. Patients were excluded if they presented with a left ventricular ejection fraction (EF) of less than 35%, acute or chronic renal insufficiency (plasma creatinine level > 150 μmol/l), liver disease, neurologic disease (with the exception of past transient ischaemic attack), as well as patients scheduled for emergency reoperation due to haemorrhage. Those exclusion criteria were chosen to allow for the exclusion of high-risk patients for prolonged postoperative intubation in the ICU.

Study V initially included 70 patients, 75 years or older, scheduled for primary elective CABG with CPB or single valve repair or replacement with CPB. Exclusion criteria included left ventricular EF of less than 30%, acute renal failure or a history of chronic renal insufficiency (plasma creatinine level > 150 μmol/l), a history of liver disease, congestive heart failure, type I diabetes mellitus, neurological disease other than transient ischemic attack (TIA), preoperative infections, obesity; body mass index (BMI) of more than 35, psychiatric disease or alcohol abuse, chronic pain syndrome, and recent use of gabapentinoids. These criteria were chosen to

exclude high-risk patients who would require prolonged intubation and, therefore, would not be able to complete the study protocol (study V/ Fig. 1)

Table 2. Summary of the demographic and clinical data of patients

	Study I (n = 41)	Study II (n = 45)	Study III (n = 160)	Study IV (n = 50)	Study V (n = 70)
Age (years)	79 ± 4	84 ± 5	73 ± 5	69 ± 14	80 ± 4
Female/Male	4 / 37	40 / 5	80 / 80	21 / 29	33 /37
Height (cm)	174 ± 8	-	167 ± 9	168 ± 10	166 ± 9
Weight (kg)	80 ± 13	-	75 ± 13	76 ± 14	74 ± 12
Pain scale	VRS, VAS	VRS,VAS RWS, FPS PQ	VRS,VAS RWS, FPS	VRS RWS	VRS
MMSE (0–30)	25 ± 3	16 ± 8	-	-	29 ± 2
GDS (0–15)	5 ± 3		-	-	-
Barthel Index (0–100)	87 ± 13	-	-	-	-
Acute pain (n)	-	20	160	50	70
Chronic pain (n)	41	25	-	-	-
Type of surgery					
Cardiac	-	-	160	50	70
Orthopaedic	-	20	-	-	-

7.2. METHODS

7.2.1. PAIN MEASUREMENT TOOLS

In studies I-V, the 5-point VRS (Melzack 1975) was used as the scale for pain assessment. In studies I-III, pain was evaluated and measured by the VAS (Scott and Huskisson 1976). In studies II-IV, the 50-cm red-coloured horizontal RWS scale (Tigerstedt and Tammisto 1988; Tarkkila and Saarnivaara 1999; Silvasti and Pitkänen 2001; Leino *et al.* 2011) was used for the measurement and evaluation of postoperative pain. In studies II-III, an FPS modified to a 7-point scale (excluding tearfulness; Bieri *et al.* 1990) was used to evaluate pain in demented patients and in cognitively normal cardiac surgery patients.

7.2.2. MCGILL PAIN QUESTIONNAIRE (MPQ) AND MINIMUM DATA SET QUESTIONNAIRE

Study II

Pain intensity was measured by using all four pain scales three times at 2-week intervals, at rest and during movement with reassessment ten minutes later. The subjects expressed the location of their pain and the movement which induced the worst pain. Patients were assessed once, before the first pain tool test, using the Finnish version (Ketovuori *et al.* 1984) of the McGill pain questionnaire (PQ). The

nurses of the department gave their observational estimate of the severity (VRS) and incidence (0 = no pain, 1 = quite rarely, 2 = daily) of pain at the time of each of the three testing sessions by using pain estimates of the Minimum Data Set questionnaire (Finne-Soveri and Tilvis 1998a).

Figure 2. Pain measurement tools

Studies I–V	Verbal Rating Scale	VRS	0= no pain, 1=slight pain, 2=moderate pain, 3=severe pain 4=unbearable pain	0–4 cm
Studies I–III	Visual Analogue Scale	VAS 10cm		0–10 cm
Studies II–IV	Red Wedge Scale	RWS		0–50 cm
Studies II–III	Facial Pain Scale	FPS		0–6

7.2.3. DETERMINATION OF THE COGNITIVE STATUS

Studies I-II and V

The cognitive status of patients was first determined by using the mini-mental state examination (MMSE) in studies I-II and V(Folstein *et al.* 1975). Thirty points was the maximum score. Only patients who were not strongly impaired cognitively (MMSE > 17) were allowed to take part in our assessment because of the assumption that such patients are likely to be able to perform the pain tests included in our protocol in study I. The mental status of the patients in study II was assessed once before the first pain tests. Cognitive status of the patients in study V was assessed before operation and on the fifth postoperative day after cardiac surgery.

7.2.4. DETERMINATION OF THE DEPRESSION

Studies I-II

For the determination of the degree of depression in the studies I-II, we used a test especially designed to detect depression in older people, the geriatric depression scale (GDS) (Yesavage *et al.* 1982). GDS is a self-reporting scale consisting of 15

yes-no items. The maximum score is 15 points, and the higher the score the greater the likelihood of depression.

7.2.5. DETERMINATION OF THE FUNCTIONAL ABILITY IN THE DAILY LIFE

Study I

The functional ability in the daily life of the patients in Study I was determined by using the Barthel Index (Mahoney and Barthel 1965; Granger *et al.* 1979a; Granger *et al.* 1979b; Reed and Gessner 1979). One hundred points is the maximum score in the Barthel Index test. The higher the score the better are the functional daily activities of the patient.

7.2.6. PROCEDURE OF PAIN MEASUREMENT IN STUDIES I-V (FIGURE 2, TABLE 3)

7.2.6.1. Community elderly in study I

Two pain scales were used to assess the intensity of pain, the VRS and the VAS. Both of these scales and the methods of assessment were meticulously described to each patient, several times as needed, until it was clear that the methods were understood. The scores on VRS were 0 "no pain", 1 "slight pain", 2 "moderate pain", 3 "considerable pain" and 4 "extreme pain" (Keele 1948; Banos *et al.* 1989). A standard 10 cm line was used as the VAS (Keele 1948; Scott and Huskisson 1976), with 0 if there was no pain and 10 if the pain was the worst imaginable by the patient. The severity of pain was first scored at rest (rest pain) by using VRS and VAS. Then the intensity of pain was determined with these tests after a particular movement of a limb or the trunk, or after a short distinct exercise, which the patient knew would provoke an increase in pain intensity (manipulation pain). All tests on an individual person were performed on the same day.

7.2.6.2. Demented patients in study II

Pain was measured 3 times at 2 week intervals by VRS, VAS, RWS, and FPS (Table 2). In order to rule out any influence of the previous pain measurements on the ongoing pain measurement, the patients were also asked to try to recall the severity of the pain in the 2-week period between measurements. In addition, the nurses of the department gave their observational estimate of the severity (VRS) and incidence (0 = no pain, 1 = quite rarely, 2 = daily) of pain at the time of each of the three testing sessions by using pain estimates of the Minimum Data Set questionnaire

(Finne-Soveri and Tilvis 1998b). The pain measurements were performed during the day. During the study period the patients received their usual pain medication. The time from the last intake of pain medication and the performance of the tests was not standardized.

7.2.6.3. Cardiac surgery patients in studies III-V

Study III

The pilot study suggested that after major surgery elderly patients become easily exhausted and are unable to reliably complete more than three pain measurement scales during one session. Thus, in addition to either RWS or FPS grouping, the patients were assessed by using both the 5-step VRS and 10-cm VAS (Table 2). The patients were studied daily for the first four days after tracheal extubation. They were provided with their eyeglasses and their false teeth prior to undergoing the pain measurements. The interview technique was standardized: before every measurement, the scale was shown to the patient and the terms (no pain – worst possible pain) were explained. Pain was assessed by always using the same words and the evaluation was made at rest and during movement (coughing or deep breathing). Each assessment of RWS and FPS was repeated after ten minutes. The pain scales were used in all the assessments in a similar order, that is, VRS, VAS, RWS or FPS.

Reasons for unsuccessful measurements were recorded during the study: the measurement was deemed unsuccessful if the patients failed to understand the testing tools. The failure measurements with VRS were as follows: a. if the patient was unable to understand questions regarding pain intensity and was unable to express the level of the pain intensity with words (0=no pain, 1=slight pain, 2=moderate pain, 3=severe pain 4=unbearable pain), b. The measurement with VAS, RWS and FPS was taken as failed, when the patient could not demonstrate their level of pain intensity on the scale. To evaluate the effect of age of compliance to pain measurement, the patients were further divided into two groups each according to their age: 65-74 and 75 years or more.

Study IV

After extubation, when the patient requested analgesia, pain intensity was measured using both the Verbal Rating Scale (VRS) and a visual 50-cm Red Wedge Scale (RWS). When the patients of study IV had postoperative pain (VRS ≥ 2, or RWS ≥ 20 cm), blood samples for the determination of the plasma concentration of fentanyl and oxycodone were taken. Pain intensity was measured regularly using the Verbal Rating Scale (VRS).

Study V

Early postoperative pain in the ICU

Pain intensity was recorded every second hour during the first 24 hours after extubation in the early postoperative period. In the ICU, 1 g of paracetamol was given intravenously as an analgesic two hours after the operation and three times daily thereafter. In the ICU, before extubation, intravenous oxycodone 0.05 mg kg^{-1} was given, as clinically indicated. When the patient expressed moderate or stronger pain (VRS ≥ 2), oxycodone was administered intravenously in the ICU (0.05 mg kg^{-1}), or orally (0.10-0.15 mg kg^{-1}) or intramuscularly (0.1 mg kg^{-1}) on the ward.

Postoperative pain 1 and 3 months after the cardiac surgery

Paracetamol was used for the treatment of postoperative pain at home. The incidence of postoperative pain was assessed by a telephone interview in which the VRS pain score at rest and during movement and the analgesics consumed were recorded one and three months after the surgery.

Table 3. Pain measurement protocols of studies I-V

Pain scales		Patient	Pain	Measurement of pain
Study I (n = 41)	**VRS,VAS**	Community-dwelling elderly	Chronic	At rest and during movement
Study II (n = 45)	**VRS, VAS RWS, FPS PQ**	Demented elderly patients	Chronic and acute	At rest and during movement
Study III (n = 160)	**VRS, VAS RWS, FPS**	Cardiac surgery elderly patients	Acute	At rest and after coughing
Study IV (n = 50)	**VRS, RWS**	Cardiac surgery elderly and middle-aged patients	Acute	Before and after analgesic
Study V (n = 70)	**VRS**	Cardiac surgery elderly patients	Acute	Before and after analgesic

7.3. ANAESTHESIA AND MONITORING DURING CARDIAC SURGERY

Studies IV-V

Patients received general anaesthesia without epidural analgesia, or local anaesthetics injected into the wound. All regular scheduled cardiac medications were administered to the patients on the morning of surgery. Patients were medicated with oral lorazepam (1-4 mg). Anaesthesia was induced with intravenous opioids followed by propofol or etomidate, and rocuronium or pancuronium was used to provide muscle relaxation. Anaesthesia was maintained with continuous infusions of propofol and fentanyl or sufentanil along with isoflurane or sevoflurane. The bispectral index (BIS) was monitored to achieve an optimal level of anaesthesia, keeping the BIS-value between 40 and 60.

CPB was performed with a roller pump, membrane oxygenator and a non-coated circuit. Non-pulsatile pump flow was maintained at 2.4 $L \cdot min^{-1} \cdot m^{-2}$ and cold blood cardioplegia was used for myocardial protection. CBP was performed under moderate hypothermia (core temperature 32-34ºC). PaCO2 was kept within the normal values according the alpha-stat principle. The revascularization procedure of off-pump CABG was performed on the beating heart with a stabilization of the target coronary arteries. When access to posterior coronary arteries was required,

Period of pain measurement	Amount of measurement	Study design
Once by two scales at rest and at movement	1	Prospective, open
Four scales 3 times at 2 weeks intervals	3	Prospective, open
Group I: VRS, VAS, RWS Group II: VRS, VAS, FPS Similar order daily measurement for the first 4 postoperative day Each RWS and FPS was repeated after 10 min.	4	Prospective, randomized, open
Pain VRS ≥ 2 , oxycodone iv, VRS and RWS measurements after 15 and 45 min after oxycodone	9	Prospective, randomized, controlled
Every second hour during the first 24 h after extubation	12	Prospective, randomized, double-blinded, placebo controlled
Postoperative pain 1 and 3 months after the cardiac surgery	2	

a suction device was used to lift the heart. Intraoperative temperatures were measured with a pulmonary artery thermodilution catheter, from the urinary bladder and the nasopharyngx .

7.4. PROTOCOL OF STUDY IV, THE ADMINISTRATION OF OPIOIDS AND SAMPLING

An arterial blood sample for the measurement of the plasma concentration of fentanyl was taken at the time when the intravenous-fentanyl infusion was stopped, and the second sample two hours later.

When the patients experienced pain after tracheal extubation (VRS ≥ 2 or RWS ≥ 20 cm), blood samples for the determination of the plasma concentration of fentanyl and oxycodone were taken. Immediately thereafter, oxycodone hydrochloride (0.05 mg/kg) was administered intravenously (= oxycodone test 1). Pain intensity and plasma concentrations of oxycodone were assessed 15 and 45 minutes after oxycodone administration. This oxycodone test was performed three times for each patient during their stay in the ICU (fig.1 /study IV) and the time interval between them was recorded.

7.4.1. DETERMINATION OF FENTANYL AND OXYCODONE CONCENTRATIONS IN PLASMA

Chemicals and reagents

Fentanyl citrate was purchased from Janssen Research Foundation (Titusville, NJ, USA) and nalorphine (internal standard) from Sigma-Aldrich Chemie Gmbh (Steinheim, Germany). Oxycodone hydrochloride was obtained from Santen Oy (Tampere, Finland). All reagents were of the highest quality.

Measurements of fentanyl and oxycodone concentration

Frozen plasma samples were thawed overnight at +5°C. Sample preparation was carried out as follows: fentanyl and oxycodone were extracted from a 1-ml aliquot of the sample by mixing with 1 ml of buffer (0.5 M $Na_2HPO_4 \cdot 2\ H_2O$) and 5 ml of toluene (containing 0.08 μg/ml of nalorphine as the internal standard). After centrifugation, the toluene layer was transferred into a clean test tube and evaporated to dryness in a vacuum evaporator. After dissolving the residue in 48 μl of butyl acetate, 12 μl of the derivatization reagent, N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) was added. Then, a 2-μl aliquot of the sample was injected into a gas chromatograph-mass spectrometer (GC-MS) (Hewlett-Packard Company, Palo Alto CA, USA) (EI, positive ions, 70 eV). The system was operated in the splitless injector mode. The DB-200 GC column was 30 m in length, had internal diameter 0.32 mm, and film thickness 0.25 (J&W Scientific Inc., Folsom, CA, USA). Helium was the carrier gas. The column temperature was initially 120°C with a hold time of 0.5 min, and it was increased 15°C/min, with a final hold time of 1 min at 340°C. The inlet and MSD transfer line heater temperatures were maintained at 250°C and 300°C, respectively. MS detection was performed in selected ion monitoring (SIM) mode. Target masses were m/z 455 for nalorphine, m/z 245 for fentanyl and m/z 495 for oxycodone.

No interfering peaks were detected in blank plasma samples. The lower limits of quantitation were set at 1.0 ng/ml for fentanyl and 2.0 ng/ml for oxycodone. At a concentration of 50 ng/ml, repeatability (relative standard deviation, RSD) was 7% for fentanyl and 11% for oxycodone, and time-different intermediate precision (RSD %) was 11% for fentanyl and 22% for oxycodone. Accuracy, expressed as percentage bias, was 3% for fentanyl and 8% for oxycodone.

7.5. PROTOCOL OF STUDY V

Patients were premedicated orally one hour before surgery with lorazepam (0.02-0.03 mg kg^{-1}) and the study drug, pregabalin 150 mg (Lyrica® 75 mg capsule, Pfizer GmbH, Freiburg, German) or placebo. The second dose of the study medication, either 75 mg of pregabalin or placebo was given on the first postoperative

day. Thereafter, the patients received either 75 mg of pregabalin or placebo twice daily until the fifth postoperative day. The hospital pharmacy performed the randomization using a computer-generated randomization schedule. The pharmacy also prepared the study medication by packing pregabalin or placebo into identical capsules for blinding. Each consenting patient received the study drug according to a consecutive randomization number, which was labeled to opaque plastic containers containing the study drugs.

7.6. POSTOPERATIVE CARE AFTER CARDIAC SURGERY

Studies III-V

Propofol sedation (2-4 $mg \cdot kg^{-1} \cdot h^{-1}$) was continued in the ICU, where analgesia was provided using paracetamol 1g intravenously. This dose was repeated every eight hours and, when needed, oxycodone in doses 0.05 $mg \cdot kg^{-1}$ was intravenously injected. Sedation was discontinued, when the central temperature reached 36°C. The tracheal tube was removed, when the patient was able to respond to verbal command and fulfilled the extubation criteria according to our clinical practice. Criteria for extubation included a responsive and cooperative patient, no uncontrolled arrhythmia, haemodynamic instability, or excessive chest tube drainage, FiO2 below 40%, pH over 7.3, and core temperature over 36.5°C, spontaneous respiratory rate less than 20 breaths/min and respiratory rate of the ventilator set at less than 2/min. The positive end-expiratory pressure was set at 6 cm H2O. The majority of patients were extubated after 6-8 hours in the ICU. When the patients did not need intensive care any more, they were transferred from the ICU to their surgical ward where they were given paracetamol 1g orally three to four times daily and oxycodone 0.1 $mg \cdot kg^{-1}$ intramuscularly or 0.2 $mg.kg^{-1}$ orally, as needed.

7.7. CONSUMPTION OF OPIODS AFTER CARDIAC SURGERY IN STUDIES III-V

In study III, the mean daily dose of intravenous oxycodone was recorded in both study groups in the ICU period. In study IV, the mean total intravenous dose of oxycodone and the mean total dose of infused fentanyl were recorded before tracheal extubation. In study V, total parenteral oxycodone consumption before tracheal extubation and thereafter as long as the patients stayed in the ICU were recorded. Total parenteral oxycodone consumption was determined during the first 16 hours after extubation. The total cumulative oxycodone consumption and orally administered oxycodone doses during the first five postoperative days were recorded.

7.8. MEASUREMENT OF POSTOPERATIVE SEDATION AND CONFUSION AFTER CARDIAC SURGERY

Study IV

Postoperative sedation was registered on the Ramsay sedation scale (Ramsay *et al.* 1974). The levels 1-6 are: 1 = patient is anxious and/or agitated, 2 = patient is co-operative, oriented and tranquil, 3 = patient responds to command only, 4 = patient responds briskly to light glabellar tap or auditory stimulus, 5 = patient responds sluggishly to tap or auditory stimuli, 6 = patient does not respond to tap or auditory stimuli. The degree of sedation was assessed concurrently with the pain intensity measurements.

Study V

Sedation scores were recorded every second hour during the first 16-24 hours after extubation or as long time as the patients stayed in the ICU. Postoperative sedation was measured with the Richmond Agitation Sedation Score (RASS) (Sessler *et al.* 2002). The scores from 0 to 9 are: 0 unarousable, 1 deep sedation, 2 moderate sedation, 3 light sedation, 4 drowsy, 5 alert and calm, 6 restless, 7 agitated, 8 very agitated, 9 combative. The degree of postoperative confusion was rated with the modified Confusion Assessment Method for the ICU (CAM-ICU) once daily during the first five postoperative days after extubation (Ely *et al.* 2001) The highest score of the modified CAM-ICU test was 25 that indicate no confusion.

7.9. FAILURE OF THE PAIN MEASUREMENT SCALES AFTER CARDIAC SURGERY IN STUDY III

The reasons for unsuccessful pain measurements were recorded after every pain measurement in cardiac surgery patients of study III/Table3.

7.10. RECORDING OF SIDE-EFFECTS; NAUSEA, VOMITING, SEDATION, AND CONFUSION AFTER CARDIAC SURGERY IN STUDIES IV-V

In study IV-V, nausea, vomiting and sedation were recorded every second hour during the first 16-24 hours after extubation or as long time as the patients stayed in the ICU. In study V, postoperative nausea and vomiting were registered by asking the patients to select one of the following descriptors: 0 = no nausea, 1 = slight nausea, 2 = moderate nausea and 3 = severe nausea. Ondansetron (4 mg i.v.) was given, when the patient had nausea or vomited.

The degree of postoperative sedation was registered with RASS (study IV) and Ramsay score (study V) according to study protocols concurrently with pain intensity measurements. Haloperidol (2.5 mg i.v.) was given, if the patient had remarkable signs or symptoms of confusion. According to our clinical protocol, these side effects were recorded also in the ward, where haloperidol or ondansetron was given, if the patients had confusion or vomiting. The total consumption of ondansetron and haloperidol were recorded at the end of the care in the ICU and at the end of the fifth postoperative day in study V. The degree of confusion was measured with the modified CAM-ICU scores once per day during five postoperative days after surgery.

7.11. LENGTH OF STAY IN THE ICU IN ELDERLY PATIENTS AFTER CARDIAC SURGERY IN STUDIES III-V

The mean length of stay in the ICU was recorded in studies III-IV.

7.12. STATISTICAL METHODS

Descriptive data were presented as mean ± standard deviation (SD), or median and range or inter-quartile rage (IQR). Patients' characteristics and clinical data were analyzed between the two study groups by paired *t*-test or Wilcoxon signed rank test for independent samples in studies I-V. Fisher´s one-sided Z-transformation was used to compare correlation coefficients in study I. The correlations between parameters were assessed using the nonparametric Spearman rank order correlation (Sigma Stat, for windows, Chicago, IL, U.S.A) in studies I-II. Also the Spearman rank order correlation was used to determine the consistency of the assessment using the four different scales, and correlation between the evaluations provided by the nurses and the pain intensity for each patient (Sigma Stat, for windows, Chicago, IL, U.S.A) in study II. The number of successful pain measurements between study groups for each measurement type was compared with the Cochran test in study III. In studies II, IV-V, the cases of the several groups were compared using analysis of variance (ANOVA) for repeated measures (Freidman´s test, study II) followed one-way ANOVA and a post-hoc test (Bonferroni, study II) (Tukey´s LDS test, studies IV-V). Statistical analyses were performed using SPSS for Windows v. 12.1 (SPSS Ltd, Chicago, Il, U.S.A) in study III.-V. If the *P* value was smaller than 0.05, the correlation between factors was considered to be statistically significant.

Table 4. Patient characteristics and intraoperative data (mean ± sd), median (range) or number of patients and P value after cardiac surgery.

	Study IV			Study V		
Variable	Elderly group (≥ 75 year) (n = 30)	Middle-aged group (≤ 60 year) (n = 20)	***P*-value**	Pregabalin group (≥ 75 year) (n = 35)	Placebo group (≥ 75 year) (n = 35)	***P*-value**
Age (years)	80 ± 14	52 ± 6	<0.001	79.5 (75-89)	79.6 (75-91)	0.92
Male/female	9/21	20/0	<0.001	21/14	16/19	0.23
Height (cm)	163 ± 29	176 ± 6	<0.001	166 ± 9	166 ± 8	0.90
Weight (kg)	72 ± 16	81 ± 14	0.025	74 ± 12	73 ± 13	0.72
Body mass index (kg/m^2)	27 ± 4	26 ± 4	0.474	27 ± 4	26 ± 4	0.56
Type of cardiac surgery						
Off-pump CABG				2	1	
CABG with CPB (n)	21	16	0.430	22	24	0.80
Valve surgery (n)	9	4		11	10	0.20
CPB time (min)	93 ± 24	97 ± 34	0.796	91 ± 17	91 ± 27	0.96
Cross clamp time (min)	65 ± 19	66 ± 27	0.642	65 ± 14	67 ± 18	0.63
Duration of anaesthesia (min)	275 ± 48	285 ± 69	0.470	302 ± 58	311 ± 104	0.67
Duration of surgery (min)	203 ± 32	222 ± 58	0.142	203 ± 32	222 ± 58	0.74
CABG with CPB (min)	206 ± 36	232 ± 58	0.101			
Valve surgery (min)	197 ± 22	185 ± 47	0.501			
Median number of bypasses	3 (2 - 6)	3 (2 -5)	0.474			
Total dose of infused fentanyl (mg)	2.3 ± 0.5	2.6 ± 0.8	0.081			
Time of extubation (min)	621 ± 313	475 ± 187	0.116	638 ± 285 *	500 ± 233	**0.04**
Total dose of oxycodone hydrochloride before extubation (mg)	9.3 ± 4.9	11.5 ± 6.4	0.175	10.8 ± 4.9 *	8.6 ± 3.5	**0.04**
Time, when VRS ≥ 2 after extubation	113 ± 128	119 ± 108	0.725			

CABG = Coronary artery by-pass grafting, CPB = Cardiopulmonary bypass, VRS = Verbal Rating Scale

8. RESULTS

8.1. DEMOGRAPHIC AND ANAESTHESIA DATA OF THE PATIENTS IN STUDIES I-V

Patient characteristics and clinical data are presented in Table 4. The total number of pain measurements was approximately 8364 in studies I-V (Table 5). Approximately 40% of pain assessments were measured with the VRS, which was used in all studies.

Table 5. Total number of pain measurements in studies I-V.

Study	Patients	VRS	VAS	RWS	FPS	Total number of pain measurement per study	
I	(n = 41)	82	82			**164**	**2.0%**
II	(n = 45)	270	270	270	270	**1080**	**12.9%**
III	(n = 160)	1280	1280	1280	1280	**5120**	**61.2%**
IV	(n = 50)	300		300		**600**	**7.2%**
V	(n = 70)	1400				**1400**	**16.7%**
Total number of pain measurement per pain scale		**3332 40.0%**	**1632 19.5%**	**1850 22.0%**	**1550 18.5%**	**8364**	

8.2. RESULTS OF PAIN MEASUREMENTS IN COGNITIVELY IMPAIRED AND DEMENTIA PATIENTS (STUDIES I-II)

Exactly 1244 pain measurements were made with four different pain scales in cognitively impaired and demented patients in studies I-II (Table 5). The mean and the median of the patients' pain intensity in cognitively impaired and demented patients at rest were mild as measured by the VRS, the VAS, the RWS, and the FPS. The pain intensity with movement was moderate in studies I-II (Table 6).

Table 6. Summary of intensity of pain on pain scales VRS, VAS, RWS and FPS at rest and movement in studies I-II.

Pain scale	Study I (n = 41)			Study II (n = 45)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range
VRS (0-4)						
at rest	1.0 ± 0.9 *	1	(0 - 3)		1	(0 – 2)
during movement	2.8 ± 0.9 *	3	(1 - 4)		2	(2 – 3)
VAS (0 -100) (mm)						
at rest	29 ± 24 *	20	(0 – 80)	23 ± 0.5		
during movement	75 ± 23 *	80	(30 -100)	59 ± 0.6		
RWS (0-50) (cm)						
at rest				13.7 ± 2.5		
during movement				31.1 ± 2.6		
FPS (0-6)						
at rest					2	(0 - 4)
during movement					4	(3 – 6)

Study I: The difference in pain intensity at rest and after movement (* $P < 0.001$, paired test)

8.2.1. PAIN SCALES VALIDITY IN COMMUNITY-DWELLING ELDERLY AND DEMENTED PATIENTS (STUDIES I-II)

Pain measurements with VRS and VAS scales at rest and movement correlated positively with each other in community-dwelling elderly. Spearman correlation coefficients between the VRS and the VAS changed from $r = 0.351$ to $r = 0.78$ ($P < 0.001$) in Study I. All four pain scales correlated with each other at rest and movement ($r = 0.392$ - 0.850, $P < 0.001$) in demented patients in study II.

8.2.2. COGNITIVE FUNCTION, DEGREE OF DEPRESSION AND ACTIVITIES OF DAILY LIFE (STUDY I)

The mean MMSE-score of the elderly in community-dwelling was 25 ± 3, the mean score on the GDS was 5 ± 4 points and the mean Barthel Index was 87 ± 13 (Table 2). VRS pain scores after movement correlated positively with the Barthel Index while VAS scores did not. The positive correlation between VRS pain scores after movement and Barthel Index was significantly different from the correlation between Barthel Index and pain at rest scored with VRS ($Z = -2.152$, $P < 0.05$) or VAS ($Z = -2.952$, $P < 0.01$) in study I.

GDS correlated positively with pain estimates given with the VRS method at rest, but not with the VAS scores at rest. After a pain-provoking movement neither VAS nor VRS pain scores correlated with GDS. Analogously, correlation coefficients between GDS and pain scored with VRS or VAS after movement were significantly different from the correlation coefficient between GDS and pain scored with VRS at rest (in both cases Z = 1.72, $P < 0.05$, Fisher's Z-transformation). Correlation coefficients between GDS and pain scored with VRS or VAS after movement did not differ from the correlation coefficient between GDS and pain scored with VAS at rest (study I).

8.2.3. CORRELATIONS BETWEEN MMSE, GDS, BARTHEL INDEX AND PAIN SCORES

The Barthel Index correlated positively with the MMSE-score and negatively with GDS. Correlation between Barthel Index and GDS differed significantly from the correlation between Barthel Index and VRS pain scores at rest (Z = -1.689, $P < 0.05$), and from the correlation between Barthel Index and pain scores after movement measured with VAS (-2.679, $P < 0.01$) or VRS (Z=-3.841, $P < 0.001$). Correlation between MMSE and the Barthel Index differed from correlations between the Barthel Index and rest pain measured with VAS (Z=2.63, $P < 0.01$) or VRS (Z=1.829, $P < 0.05$) in study I.

8.2.4. MMSE SCORES AND PAIN MEASUREMENTS IN DEMENTED PATIENTS (STUDY II)

The higher the MMSE scores (24-30), the better the patients were able to use the pain scales for reporting their pain. However, even slight cognitive impairment (MMSE 17-23) induced difficulties in using RWS, VAS and FPS. Moderately (MMSE 11-16) and severely (MMSE ≤ 10) demented patients could report better the severity of pain using the VRS method in comparison with the others: in the patients with the lowest MMSE (≤ 10), the success rate of measurement with the RWS was less than 26%, on average. The antipsychotic drugs were used more in the group of the lowest MMSE ≤ 10 as compared to the other groups ($P < 0.05$).

8.2.5. THE SEVERITY AND INCIDENCE OF PAIN ESTIMATED BY NURSES (STUDY II)

The severity and incidence of pain in demented patients estimated by nurses did not correlate consistently with the patients' magnitude of pain measured with the

four tools. However, in all three sessions, the nurses' estimates of the intensity of the patients pain correlated positively with their own estimates of the incidence of patient's pain (r = 0.474-0.515, P < 0.01) in Study II.

8.3. EVALUATION OF PAIN SCALES AND PAIN INTENSITY IN ELDERLY PATIENTS AFTER CARDIAC SURGERY (STUDIES III-V)

Exactly 7120 pain measurements with four different pain scales were performed in elderly patients after cardiac surgery (Table 5). Pain intensity was mostly mild at rest and the maximal pain intensity was usually assessed as moderate after coughing during the first three days for all pain scales (VRS, VAS, RWS, FPS) in study III (Table 7). The incidence and intensity of early postoperative pain measured with VRS within 24 hours after extubation in studies IV-V is shown in Table 8. Incidence of moderate pain altered from 4 to 39% in elderly patients and from 10 to 40% in middle-aged patients during the early postoperative period after cardiac surgery in studies IV-V (Table 8). Pain intensity was primarily measured just before or after analgesic. The applied clinical protocols for postoperative pain management were consistent for studies III-V.

8.3.1. ASSESSMENT OF PAIN AFTER CARDIAC SURGERY IN ELDERLY PATIENTS (STUDIES III-IV)

The failure rate of pain measurement was the highest for all the scales during the first two postoperative days after tracheal extubation. The percentages of successful pain measurements were VRS 87%, 10-cm VAS 62%, RWS 76% and FPS 60% on the first day after tracheal extubation. The patients succeeded with all pain scales better during the following next three days. The most common reasons for the unsuccessful measurements were postoperative confusion, exhaustion and difficulties to interpret the scales. The higher age decreased the successful pain measurements. In the group over 75 years of age (≥ 75 years), VRS (81%) and RWS (83%) scales were used most reliably. During the first day after extubation, the pain measurement with 10-cm VAS succeeded in 60% of the patients with FPS in only 44% of cases.

The reasons for elderly pain-measurement failures were postoperative confusion, exhaustion, delirium, or unwillingness to answer after cardiac surgery (study III). The use of the VRS was successful in 99% of the pain measurements for the older (≥ 75 years) and the younger (≤ 60 years) groups in study III. The percentage of the successful pain measurements during study III with RWS was 69% in the older group and 95% in the younger group.

8.3.2. PAIN SCALES VALIDITY IN THE ELDERLY AFTER CARDIAC SURGERY (STUDY III)

Spearman correlations included 16 pairs between successful measurement with the RWS and the FPS pain scales and the control pain scales with the VRS and the VAS in study III. All pain scales at each rating correlated well over the four day assessment period. Pain measurement with the RWS correlated with the VAS (r = 0.758, P < 0.001) and a weaker correlation was seen between the RWS and the VRS (r = 0.666, P < 0.001). There was also a good correlation between the measurements with FPS and the VAS (r = 0.873, P < 0.001) and weaker correlation with the VRS was found (r = 0.583, P < 0.001). There was also a good correlation between the initial measurement and the second measurement that followed the 10 min rest period ((r = 0.898-1.00, P < 0.001).

Table 7. Results of assessment of pain scales in elderly patients after cardiac surgery (study III) Pain intensity at rest and during movement, after coughing or deep breathing, were measured on the four days (1-4 day) after extubation.

	1st day at rest	2nd day at rest	3rd day at rest	4th day at rest
VRS	1.0 (0-4) n=136	1.0 (0-3) n=143	1.0 (0-4) n=14	0 (0-2) n=143
VAS	2.0 ± 1.8 n=97	1.8 ± 1.7 n=115	1.6 ±1.9 n=126	0.8 ±1.2 n=123
RWS	13 ± 11 n=61	11 ± 9 n=66	10 ± 9 n=66	6 ± 8 n=66
RWS (10 min)	12 ± 12 n=41	10 ± 10 n=49	9 ± 9 n=50	7 ± 9 n=51
FPS	1.0 (0-3) n=46	1.0 (0-4) n=60	1.0 (0-5) n=63	0.0 (0-3) n=6
FPS (10 min)	1.0 (0-3) n=39	1.0 (0-4) n=48	1.0 (0-5) n=52	0.0 (0-5) n=55
	1st day movement	**2nd day movement**	**3rd day movement**	**4th day movement**
VRS	2 (0-4) n=135	2 (0-4) n=142	2 (0-4) n=148	1 (0-3) n=143
VAS	4.3 ± 2.6 n=97	4.4 ± 2.2 n=115	3.8 ± 2.2 n=125	2.6 ± 3.4 n=122
RWS	25 ± 12 n=61	23 ± 10 n=66	22 ± 10 n=67	16 ± 11 n=66
RWS (10 min)	12 ± 12 n=41	10 ± 9 n=49	9 ± 9 n=50	7 ± 9 n=51
FPS	3 (0-5) n=46	2 (0-5) n=59	2 (0-5) n=63	1 (0-5) n=64
FPS (10 min)	2 (0-5) n=39	2 (0-5) n=48	2 (0-5) n=52	1 (0-5) n=55

VRS = Verbal Rating Scale, VAS = Visual Analogue Scale 0-10 cm, RWS = Red-Wedge-Scale 0 – 50 cm, FPS = Facial Pain Scale. RWS 10 min = Red Wedge Scale measurement after 10 min from the initial measurement. FPS 10 min = Facial Pain Scale measurement after 10 min from the initial measurement. Values of VRS and FPS are median (range). Data are expressed as mean ± sd (VAS and RWS) or median (range) (VRS and FPS)

Table 8. The percentage of patients with different levels of pain intensity measured by Verbal Rating Scale VRS (0-4) after oxycodone.

Study period	Pain VRS (0-4)	Study IV Elderly group **Percentage (%)**(≥ 75 yrs), (n=30)	Middle-aged group **Percentage (%)** (≤ 60 yrs) (n=20)	***P*-value**	Time after extubation	Pain VRS (0-4)	Study V Pregabalin group (≥ 75 yrs) **[n (VRS ≥ 2)** / n / **%]**	Placebo group (≥ 75 yrs)	***P*-value**
1	VRS 15 min 0	50	30	NS	0 h	**VRS ≥ 2**	**6**/31/**19%**	**10**/31/**32%**	NS
	1	37	45						
	2	**10**	**20**						
	3	**3**	**5**						
	4	**0 13% VRS ≥ 2**	**0 25% VRS ≥ 2**	**0.037**	2 h	**VRS ≥ 2**	**4**/31/ **13%**	**12**/32/**37%**	**0.041**
	VRS 45 min 0	50	20						
	1	37	55						
	2	**13**	**20**						
	3	**0**	**5**		4 h	**VRS ≥ 2**	**7**/30/**23%**	**8**/32/**25%**	NS
	4	**0 13% VRS ≥ 2**	**0 25% VRS ≥ 2**						
2	VRS 15 min 0	50	40	NS					
	1	30	40						
	2	**20**	**10**		6 h	**VRS ≥ 2**	**4**/31/ **13%**	**9**/32/**28%**	NS
	3	**0**	**10**						
	4	**0 20%VRS ≥ 2**	**0 20% VRS ≥ 2**						
	VRS 45 min 0	50	35	NS					
	1	37	25		8 h	**VRS ≥ 2**	**6**/31/**19%**	**7**/30/**23%**	NS
	2	**6.5**	**20**						
	3	**6.5**	**5**						
	4	**0 13% VRS ≥ 2**	**5 30% VRS ≥ 2**						
3	VRS 15 min 0	55	40	NS	10 h	**VRS ≥ 2**	**3**/29/**10%**	**11**/29/**38%**	**0.029**
	1	41	50						
	2	**4**	**5**						
	3	**0**	**5**						
	4	**0 4% VRS ≥ 2**	**0 10% VRS ≥ 2**	**0.008**	12 h	**VRS ≥ 2**	**4**/28/**14%**	**10**/28/**39%**	**0.034**
	VRS 45 min 0	57	25						
	1	33	35						
	2	**10**	**40**						
	3	**0**	**0**		16 h	**VRS ≥ 2**	**3**/20/ **15%**	**9**/23/**39%**	NS
	4	**0 10% VRS ≥ 2**	**0 40% VRS ≥ 2**						

8.4. THE CONCENTRATION OF FENTANYL AFTER CARDIAC SURGERY (STUDY IV)

At the end of surgery and two hours later, the mean plasma concentrations of fentanyl were significantly higher in the older patients than in the younger ones (P <0.05). Fentanyl was still detected in the plasma of some patients after extubation at the time of beginning the first oxycodone test, with concentrations of 1.43 ± 0.94 ng/ml in the older group (n = 12/30) about 12 hours after the end of the fentanyl infusion, and correspondingly 1.36 ± 0.67 ng/ml in the younger group (n = 8/20) about 10 hours after the end of the fentanyl infusion.

8.5. OXYCODONE ADMINISTRATION AFTER CARDIAC SURGERY IN STUDIES IV-V

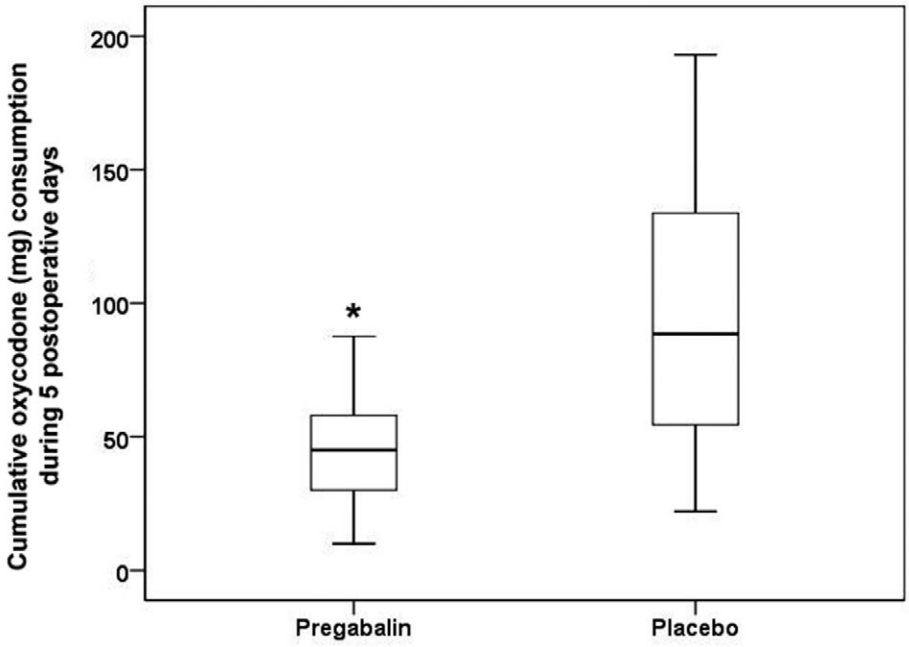
Study IV

Prior to tracheal extubation in the ICU, the mean cumulative oxycodone dose was 9.3 ± 4.9 mg in the older group (≥ 75 years) and 11.5 ± 6.4 mg in the younger group (≤ 60 years) (NS). The mean plasma concentrations of oxycodone with the three tests were not statistically different between the older and the younger groups. The time interval between the first and second oxycodone test was similar between the groups, but the interval between the second and third oxycodone test was significantly longer in the older group (263 ± 160 min) than in the younger group (182 ± 78 min) (P < 0.05).

Study V

Mean cumulative parenteral consumption of oxycodone during the first 16 postoperative hours after extubation was 43% lower in the pregabalin group (8 ± 5 mg) compared to the placebo group (14 ± 6 mg) (P < 0.001). Mean cumulative total oxycodone consumption from extubation to the end of the fifth postoperative day was 48% lower in the pregabalin group (48 ± 28 mg) compared with the placebo group (93 ± 44 mg) (P < 0.001). Cumulative consumption of oral oxycodone after extubation to the end of the fifth postoperative day was 53% lower in the pregabalin group (30 ± 25 mg) than in the placebo group (64 ± 41 mg) (P < 0.001; Figure 4). Consumption of oral oxycodone was lower in the pregabalin group during the first three postoperative days.

Figure 4. Effect of pregabalin in elderly patients during five postoperative days after cardiac surgery* P < 0.05 between the groups



8.6. LEVEL OF SEDATION AND POSTOPERATIVE CONFUSION IN ELDERLY PATIENTS AFTER CARDIAC SURGERY

Study III

The incidence of delirium, confusion and exhaustion varied from 7.0% to 1.4% in elderly patients during four postoperative days after cardiac surgery. The most common reasons for the failure of the pain measurement were postoperative confusion, exhaustion and delirium.

Study IV

By 15 min after administration of oxycodone (0.05 mg/kg i.v.) the degree of sedation was more intense in the older patients (≥ 75 years) as compared with in younger group (≤ 60 years) ($P < 0.05$). Still, after 45 min from the administration of an oxycodone bolus the elderly patients were more sedated than the younger patients ($P < 0.05$). There was on average a two-hour longer time to extubation in the older group (≥ 75 years) than in the younger patients (≤ 60 years) in study IV (P = NS). During the study period no patients displayed signs and symptoms of postoperative delirium.

However during their stay in the ICU, one (5%) patient from the younger group (≤ 60 years) and five (17%) of the older group (≥ 75 years) suffered from delirium.

Study V

One patient (1%) was excluded from the study because of preoperative delirium. Two patients (3%) (≥ 75 years) in study V displayed delirium which prolonged their stay in the ICU. The sedation scores on RASS were not different between the groups, except at two hours after extubation, when the patients in the pregabalin group were less sedated than those in the placebo group ($P < 0.05$) (Table 9). The CAM-ICU confusion test score was reduced in the placebo group on the first day after extubation in study V (Table 10, $P < 0.05$). The number of patients who received haloperidol either in the ICU or on the ward did not differ between groups.

8.7. SIDE-EFFECTS, NAUSEA AND VOMITING, AND COMPLICATIONS IN ELDERLY PATIENTS AFTER CARDIAC SURGERY (STUDIES IV-V)

The incidence of nausea and vomiting in elderly patients was consistent (34-37%) in studies IV and V after cardiac surgery. Approximately 36% of elderly patients and 25% of middle-aged patients suffered from postoperative vomiting in study IV, whilst 34% of patients in the pregabalin group and 37% of patients in the placebo group had postoperative nausea during the first 16 hours after extubation in study V. Furthermore, 31% of patients in the pregabalin group and 25% in the placebo group vomited during the 16 hours following extubation in study V. The incidence of nausea and vomiting and the number of patients receiving antiemetics did not differ between groups (Table 4). The incidence of postoperative stroke was 4.3% (3/70) in the study V. All patients with this complication were in the pregabalin group, where the incidence of stroke was 8.6%.

8.8. LENGTH OF STAY IN THE ICU FOR ELDERLY PATIENTS AFTER CARDIAC SURGERY (STUDIES III-V)

The mean duration of stay in the ICU of the patients in studies III-V are presented in Table 10. Four patients from the elderly group in study IV had a prolonged ICU stay (> 48 hours) due to postoperative complications: one pneumonia, two low-output syndromes and one delirium and respiratory failure. One patient with unstable haemodynamic status and two patients with confusion and postoperative delirium stayed in the ICU for 5 postoperative days in study V.

8.9. POSTOPERATIVE PAIN ONE AND THREE MONTHS AFTER CARDIAC SURGERY (STUDY V)

Peri- and postoperative administration of pregabalin reduced the incidence of postoperative pain in elderly patients at three months after cardiac surgery. Patients in the placebo group experienced pain during movement significantly more often than patients in the pregabalin group (23% vs 4%, $P < 0.05$).

Table 9. Patient postoperative data of sedation, postoperative confusion and vomiting after extubation (mean ± sd, median (range) or number of patients and P value after cardiac surgery.

Variable	Study IV Elderly group (≥ 75 year) (n = 30)	Middle-aged group (≤ 60 year) (n = 20)	*P*-value	Study V Pregabalin group (≥ 75 year) (n = 35)	Placebo group (≥ 75 year) (n = 35)	*P*-value
Ramsay score						
Test 1 at 0 h	2 (2 – 5)	2 (2 – 4)	0.122			
15 min	2 (2 – 5)	2 (0 – 4)	0.272			
45 min	2 (2 – 5)	2 (2 – 4)	0.424			
Test 2 at 0 h	2 (2 – 5)*	2 (2 – 4)	**0.007**			
15 min	2 (2 – 5)	2 (2 – 4)	0.221			
45 min	2 (2 – 4)	2 (2 – 4)	0.150			
Test 3 at 0 h	2 (2 – 4)	2 (2 – 3)	0.075			
15 min	2 (2 – 5)*	2 (1 – 3)	**0.022**			
45 min	2 (2 – 4)*	2 (1 – 4)	**0.035**			
RASS score at 0 h				5 (4 – 5)	5 (0 – 6)	0.42
2 h				5 (3 – 5)	5 (3 – 9) *	**0.02**
4 h				5 (3 – 5)	5 (0 – 6)	0.87
6 h				5 (4 – 6)	5 (3 – 6)	0.40
8 h				5 (4 – 5)	5 (3 – 5)	0.18
10 h				5 (4 – 6)	5 (0 – 5)	0.62
12 h				5 (4 – 5)	5 (4 – 5)	0.57
16 h				5 (4 – 5)	5 (4 – 5)	0.45
CAM-ICU scores						
postoperative day 1				24 (14 – 25) *	21 (0 – 25)	**0.04**
postoperative day 2				24 (15 – 25)	23 (0 – 25)	0.13
postoperative day 3				25 (17 – 24)	25 (20 – 25)	0.92
postoperative day 4				25 (21 – 25)	25 (19 – 25)	0.93
postoperative day 5				25 (23 – 25)	25 (25 – 25)	0.31
Postoperative vomiting (n)	11/30 (37%)	5/20 (25%)	0.597	13/32 (34%)	12/32 (37%)	0.43

RASS= Richmond Agitation Sedation Score (0 – 9), CAM-ICU=Confusion Assessment Methods for Intensive Care Units scores (0 – 25)

Table 10. Postoperative length of stay in the ICU and ıe hospital (mean ± sd) for elderly patients after cardiac surgery (studies III-V

Study III			Study IV			Study V		
RWS group (≥ 65 year) (n = 80)	FPS group (≥ 65 year) (n = 80)	*P*-value	Elderly group (≥ 75 year) (n = 30)	Middle-aged group (≤ 60 year) (n = 20)	*P*-value	Pregabalin group (≥ 75 year) (n = 35)	Placebo group (≥ 75 year) (n = 35)	*P*-value
Postoperative LOS in the ICU (days)								
2.1 ± 1.5	2.2 ± 1.7	NS	2.0 ± 1.7*	1.0 ± 0.5	**0.020**	1.5 ± 0.8	1.5 ± 1.1	0.73
Postoperative LOS in the hospital (days)								
						7.5 ± 3.1	8.1 ± 2.9	0.43

RWS = Red Wedge Scale, FPS = Facial Pain Scale, LOS = Length of St , ICU = Intensive Care Unit

9. DISCUSSION

9.1. CLINICAL RESEARCH IN ELDERLY

The measurement and the management of pain in cognitively impaired patients in long-term hospital care and cognitively normal elderly after cardiac surgery have been investigated in these clinical studies I to V. The mean age of these patients was high, 77 years.

In general, the elderly patients are often excluded from clinical research. Thus, the under-representation of older people in clinical research is accepted practice. This tendency lies in direct contrast to the forecast of an aging global population, that trends toward an older overall population in the future. Indeed, elderly people undergo more frequent surgeries and anaesthetic procedures than younger patients (McMurdo *et al.* 2005; Rooke *et al.* 2002; Bayer and Tadd 2000). One third of studies published in four major medical journals excluded older people without justification in 1997 (Bugeja *et al.* 1997). This analysis was repeated for papers published in the same journals in 2004. Almost 15% of papers still unjustifiably excluded older people, and fewer than 5% of the research published was specific to older people (McMurdo *et al.* 2005). Therefore, there is a huge difference today between the real clinical world and the middle-age patients who participate in clinical studies.

The elderly patients are excluded for many reasons, despite the fact that the elderly demonstrate a high rate of willingness to consider participation in clinical trials. It is well known, that the elderly may have many risk factors for drug interactions, side effects, re-admission and high drop out rates, all of which may fail to flatter findings. In addition, there are some important ethical viewpoints when including the elderly in clinical studies. Researchers should ensure that the elderly are able to understand the purpose of the study and responsibly confirm the patient's cognitive status. It is often a difficult question whether elderly patients with mild cognitive impairment should be considered in clinical trials. Many elderly wish to inform and discuss the study with relatives before enrolling. Furthermore, visual, hearing and cognitive impairments can complicate the patient´s cooperation with the clinical staff. Therefore, the researchers must be patient, careful and progress slowly with the elderly patients.

However, it is important to increase the the amount of data being retrieved from studies on older patients. It cannot be assumed that the benefits to younger patie-

nts enrolled in trials can be extrapolated to the more frail older patients (Bell *et al.* 1987). All elderly patients have age-related physiological changes that affect many pharmacological parameters. However, it is not the age, which causes the changes in elderly. The general physiological and health conditions are the most important factors, which makes the remarkable differences between elderly patients. This aspect makes the clinical research work more challenging in the older population.

The number of the patients in primary long-term care increases every year in Finland (Finne-Soveri and Tilvis 1998a). Additionally, more elderly patients require cardiac surgery. One fourth of cardiac surgery patients is aged 75 years or over in Helsinki University Hospital in Finland (Suojaranta-Ylinen *et al.* 2006). The investigation reported here has originated from our clinical interest to improve pain measurement and postoperative pain management for the elderly patients in our clinics. The elderly were involved in these studies willingly and they were very interested and well-motivated to cooperate with the researchers. Only seven of the cardiac surgical patients (2%) refused to participate in the studies.

9.2. PAIN INTENSITY IN THE ELDERLY (STUDIES I-V)

Pain intensity for all study patients was measured with the VRS, however the RWS, the VAS and FPS were also used in studies I-IV. (Table 6-7). The prevalence of pain experienced by elderly patients at Rehabilitation Hospital Oulunkylä and at Primary Care Hospital Katriina was not determined. Only patients who suffered daily pain (study I-II), were recruited for these studies. A cross-national study in Finland, Italy and the Netherlands has shown that the prevalence of pain in institutionalized elderly people was 57.1% in Finland, 32.2% in Italy and 43% in the Netherlands (Finne-Soveri and Tilvis 1998a; Achterberg *et al.* 2010). A Scandinavian study compared pain prevalence, characteristics and clinical correlates among patients in long-term care in Denmark, Sweden, Finland and Iceland. The results showed, that 22-24% of the residents suffered daily observable pain (Finne-Soveri *et al.* 2000). Persistent and chronic pain was highly prevalent with associated negative effects on daily function and quality of life. However, our study showed that mild chronic pain reduced daily activities less than cognitive dysfunction or depression in community-dwelling Finnish elderly (study I). However in the previously performed cross-national study, an association between pain and cognitive impairment was not found (Finne-Soveri *et al.* 2000).

The intensity of pain was mainly mild in our studies for long term care patients (studies I-II). They experienced mild pain, although the elderly were given their pain killer regularly during the study. It is a well-documented problem in many studies that chronic pain is not very well treated in elderly nursing home residents (AGS

Panel on Persistent Pain in Older Persons 2002; Allcock *et al.* 2002).

According to our clinical protocol after cardiac surgery, an analgesic was always administered when patients expressed moderate or stronger pain (VRS ≥ 2). Elderly surgical patients expressed mostly mild pain at rest, but they reported moderate pain after coughing (study III). However, the incidence of the moderate or strong pain was momentarily high (40 %) before the administration of analgesic medication in studies IV-V, despite a clinical protocol for pain treatment. This finding is similar to a previous investigation, which found that the intensity of cardiac surgical pain fluctuated between moderate to severe pain (Meehan *et al.* 1995; Ferguson *et al.* 1997; Yorke *et al.* 2004). This indicates that pain management still requires improvement for issues such as more precise pain assessment, the timely administration of opioids and the better communication of pain experience between the health care professionals and the patients.

In this study, the pain intensity of the elderly was strongest during the first three postoperative days after surgery (study III). Correspondingly, the consumption of opioids was as highest during same time period on the first three days after cardiac surgery in study V, which was similarly observed by Müller et al. (Mueller *et al.* 2000).

9.3. PAIN MEASUREMENT IN THE ELDERLY (STUDIES I-V)

The present studies I-III evaluated the pain measurement tools in Finnish elderly patients. These studies showed that all four scales (VRS, VAS, RWS, and FPS) are reliable and valid pain tools for assessing chronic and acute pain in Finnish elderly people. However, the VRS was the most applicable and the most sensitive pain scale in our clinical settings in demented elderly patients and in cognitively normal elderly after cardiac surgery. Recently, the VRS and RWS have been reported to be the best pain measurement scales in Finnish elderly patients with hip fracture or other lower limb trauma (Leino *et al.* 2011). Thus, the results of this study are comparable with our findings, which indicated that the RWS is also an applicable pain scale for elderly patients after cardiac surgery (study III). Comparatively, Li et al. have investigated postoperative pain assessment with three pain intensity scales in Chinese elders. The Iowa Pain Thermometer (IPT) was the most practical choice based on patients' preference (Li *et al.* 2009). Their comparison of four pain scales in Chinese adults showed that the FPS-R appeared to be best assessment, followed by the NRS and the VDS (Li *et al.* 2007). Although the FPS has been reported in other studies as reliable and valid for older adults (Herr *et al.* 1998; Taylor and Herr 2003; Kim and Buschmann 2006), in our studies the FPS was not an ideal tool for pain assessment in Finnish elderly patients; nor was the VAS, which ap-

peared to be more unreliable than the VRS and RWS (studies II-III). Therefore, the evaluation of the pain scales should be researched for validity across cultural and linguistic groups. Culture influences how each person experiences and responds to pain, including how and when to request treatment (Melzack 1975; Melzack 1987; Campbell *et al.* 2005; Dworkin *et al.* 2009).

Our studies also confirm that the VAS, typically regarded as the gold standard of pain measurement, was not considered to be the best choice in Finnish elderly patients, including those with mild-to moderate impairment and postoperative delirium and confusion. The VRS had a good profile with low error rates compared to the VAS in studies II-III. The difficulties with the use of the VAS among the elderly have also been documented previously in the other studies (Gagliese *et al.* 2005; Hadjistavropoulos *et al.* 2007; Leino *et al.* 2011). However, Breivik et al published a report where the four-point VRS seemed to underestimate intense pain when compared to the VAS (Breivik *et al.* 2000).

Although many new pain scales have been developed and numerous clinical pain research works have been published on demented patients (Fuchs-Lacelle and Hadjistavropoulos 2004; Graham *et al.* 2004; Pautex *et al.* 2005; Herr *et al.* 2006a; Herr *et al.* 2006b; Pautex *et al.* 2006; Hadjistavropoulos *et al.* 2007; Kaasalainen 2007; Shega *et al.* 2007; Breivik *et al.* 2008; Fuchs-Lacelle *et al.* 2008; Haasum *et al.* 2011) or the elderly after non-cardiac surgery, many practical problems remain regarding assessment and documentation of acute or chronic pain in elderly patients in primary care and in the immediate postoperative phase after surgery (Aubrun 2005; Gagliese *et al.* 2005; Aubrun and Marmion 2007). The results of study II clearly demonstrated that the VRS is useful in cognitively normal elderly and demented Finnish patients (MMSE $\geq$ 17). Approximately 62% of the severely demented patients with the lowest MMSE (< 10) were able to express their pain intensity with the VRS. Previous studies have reported similar findings, in that the VRS is a practical self-reporting assessment tool to measure pain in cognitively impaired patients (Closs *et al.* 2004; Hadjistavropoulos *et al.* 2008).

Study III may be the first research ever to evaluate and compare the pain scales in elderly patients after cardiac surgery. The VAS is the most commonly used tool for the assessment of pain in the routine clinical setting and scientific work, although the measurement of pain with VAS has been validated poorly, for example in elderly cardiac surgical patients (Mueller *et al.* 2000; Lahtinen *et al.* 2002; Rapchuk *et al.* 2010). The findings presented here indicate that the VRS is a more reliable pain scale than the VAS for use after cardiac surgery. The number of successful pain measurements with the VAS was 24% lower compared to the VRS. The reasons for the poor success rate with the VAS pain measurements were related to postoperative confusion, delirium, and the deep sedation seen in elderly patients. Furthermore, a higher age has been associated with a high frequency of failure rates

for the use of the VAS (Gagliese and Katz 2003; Fassoulaki *et al.* 2005; Gagliese *et al.* 2008; Leino *et al.* 2011).

The choice of the pain assessment tools in study IV was based on the results of studies II and III, where the VRS and the RWS were the best tools for chronic pain measurement in cognitively impaired and for postoperative pain measurement in Finnish elderly. However, the results of study IV indicated that the elderly had considerable difficulties in expressing their pain after cardiac operations by using the visual RWS scale, although the RWS was initially developed for measuring the intensity of postoperative pain in the recovery room in Finnish patients who received general anaesthesia (Tigerstedt and Tammisto 1988). Also, the RWS has been used for postoperative pain measurement in Finnish elderly orthopedic patients (Silvasti and Pitkänen 2001). It remains speculative as to why the elderly patients did not manage to use the visual pain scales during the early postoperative period after cardiac surgery. Perhaps, the influences of anaesthesia agents as well as opioids and CPB may impair the ability to interpret the visual pain scales just after tracheal extubation. In this respect, it was probably logical to measure the pain intensity only with the VRS in study V.

New findings from these studies demonstrated that the VRS might be a good choice to measure acute pain in cognitively normal elderly and chronic pain in cognitively impaired elderly. Both cognitively normal elderly after cardiac surgery and cognitively impaired elderly with chronic pain have difficulties in expressing their pain with visual pain scales (i.e. the VAS, the RWS, and the FPS).

9.4. THE SEVERITY AND INCIDENCE OF PAIN ESTIMATED BY THE NURSES IN ELDERLY PATIENTS

In study II, the incidence and severity of pain estimated by the nurses did not correlate with the patients' pain intensity as measured with the four tools. This finding indicates that the communication of pain experience between the cognitively impaired patients and nursing staff remains challenging. The demented patients may be unable or unwilling to express their pain. Nursing staff have a hectic day schedule and pain control can become a secondary consideration to the greater volume of nursing work. Additionally, other researchers have reported that the health care professionals tend to underestimate pain in demented patients (Pautex *et al.* 2005), as well as after cardiac surgery (Watt-Watson and Stevens 1998). Based on the results of study II, the VRS appears to be a good choice for the clinical assessment of pain in the elderly. Pain control should be performed at regular time points and individually, when the patient is likely to suffer from pain and when the patient complains of pain. In addition, pain should always be measured before and after

the administration of pain medication, mobilization, physiotherapy, during daily activities and the nursing procedures which may cause pain. It is very important to know the intensity of patients' pain over time instead of knowing only whether pain is present or not (Cleeland and Ryan 1994). Nowadays, most hospitals have an Acute Pain Services (APS). This organization with pain nurses and anesthesiologists have improved postoperative pain management. They are also responsible for educating for health care staff involveded in postoperative care. The intensity of postoperative pain in middle-aged patients on the ward has been reported to decrease by the implementation of a nurse-based pain service with an acute pain nurse (Salomäki *et al.* 2000).

9.5. EFFECT OF FENTANYL IN THE ELDERLY AFTER CARDIAC SURGERY

In study IV, at the end of the cardiac surgery performed under anaesthesia with intravenous fentanyl and an inhalational agent, the plasma concentration of fentanyl was higher after the discontinuation of fentanyl infusion and two hours later in elderly patients in comparison with those of younger adult patients. The current emphasis on fast recovery, early tracheal extubation and a short stay in the ICU demands a great precision in administering fentanyl in the elderly. Fentanyl is still widely used as a potent intraoperative analgesic agent with hypnotic drugs for non-cardiac and cardiac surgery in all aged patients (Ahonen *et al.* 2000; Hudson *et al.* 2002; Myles *et al.* 2002; Silbert *et al.* 2006). The first studies of the pharmacokinetics of fentanyl in the elderly were published by Bentley et al., and Scott and Stanski, in the early 1980s; who described that some of fentanyl´s pharmacokinetic variability with respect to clearance could be aged related (Bentley *et al.* 1982), although this conclusion has not been verified (Scott and Stanski 1987; Singleton *et al.* 1988). The current investigation indicates that the risk of fentanyl accumulation after continuous infusion is higher in elderly than in middle aged patients. This result is consistent with previous studies that showed accumulation of fentanyl after buccal administration in healthy volunteers (Clark *et al.* 2004; Darwish *et al.* 2008). Recent studies found that patients have better and faster recovery after cardiac surgery when they receive morphine as compared with fentanyl. Fentanyl presents no benefits over morphine in terms of the duration of tracheal intubation, length of stay in the critical care unit, or period of hospitalisation (Myles *et al.* 2000; Murphy *et al.* 2009). In addition, it has been published that, in comparison to fentanyl, morphine improves myocardial function and reduces inflammatory markers after cardiopulmonary bypass (Murphy *et al.* 2007). The future of fentanyl in cardiac anaesthesia can only be resolved with time and more research. To assess

its potential, larger, randomized studies are required, where elderly patients and patients undergoing more demanding surgeries are included.

9.6. EFFECT OF OXYCODONE AND POSTOPERATIVE PAIN MANAGEMENT IN THE ELDERLY AFTER CARDIAC SURGERY

There was no difference in the plasma concentrations of oxycodone between elderly (≥ 75 years) and middle-aged (≤ 60 years) patients after oxycodone doses (0.05 mg/kg i.v.). However, the elderly retained painlessness for longer and were more deeply sedated after the second bolus. The results presented here indicate that the elderly are more sensitive to the analgesic action of oxycodone and the clearance of oxycodone is slower in the elderly. There are a relatively small amount of studies into the use of oxycodone in the elderly; Villesen et al. have demonstrated the pharmacokinetics of morphine and oxycodone following intravenous administration to elderly patients after hip surgery (Villesen *et al.* 2007). They reported that the elderly had a great variability in the individual pharmacokinetic parameters for both opioids, however they did not find any changes in the pharmacokinetic parameters of morphine and oxycodone following intravenous administration in elderly patients compared with younger healthy volunteers. Additionally, Kaiko *et al.* did not document any significant difference in the AUC of a single 20 mg oral dose of controlled-release oxycodone between young (< 45 years) and older (> 65 years) patients (Kaiko *et al.* 1996). Similar findings have been published by Cherrier et al. (Cherrier *et al.* 2009).

9.7. OPIOIDS SIDE EFFECTS IN THE ELDERLY AFTER CARDIAC SURGERY

9.7.1. OVER SEDATION, CONFUSION, AND DELIRIUM

The results of studies III-V indicate that old age is a risk factor for over sedation, confusion, and postoperative delirium after cardiac surgery. Acute changes in cognition and attention after cardiac surgery are a well-documented multilateral problem. Pre-existing cognitive dysfunction is one of the strongest predictors of the development of postoperative delirium. The incidence of postoperative delirium varied from 3 to 73% depending in the type of cardiac surgery (Sockalingam *et al.* 2005).

Prevention of delirium is important especially in the elderly. The optimization of analgesics and pain control has a marked impact on patient comfort and prevention of confusion and delirium (Herrick *et al.* 1996). The findings of study IV indicated

that the elderly were more sedated and had less pain after oxycodone doses during the early postoperative period after extubation. Study V, suggested that the opioid sparing-effect of pregabalin decreased postoperative confusion in elderly patients on the first postoperative day after extubation. Based on these observations, it is important to avoid the high doses of opioids in elderly patients. The stricter clinical guidelines and protocols for regular pain measurement and the assessment of the level of sedation could lead individual opioid dosing in elderly patients. The result might be less oversedation, confusion and delirium postoperatively in the elderly.

9.7.2. POSTOPERATIVE NAUSEA AND VOMITING

The prevalence of nausea and vomiting (PONV) in elderly patients varied from 34% to 37% in studies IV and V. In earlier studies, the overall incidence of PONV in patients undergoing cardiac surgery was higher (45-50%) than in our investigation (Grebenik and Allman 1996; Woodward *et al.* 1999). One risk factor for PONV is age under 60 years (Kogan *et al.* 2003); our results are in agreement with that finding.

9.8. THE OPIOID SPARING EFFECT OF PREGABALIN IN ELDERLY

This was the first study where the opioid sparing effect of pregabalin was investigated in elderly patients after cardiac surgery. Our findings indicated that the administration of pregabalin reduced the incidence of postoperative confusion on the first postoperative day, but pregabalin increased the time to extubation. In addition, pregabalin-treated elderly had less pain in early postoperative period and during movement at three months after cardiac surgery.

Several studies have demonstrated the opioid-sparing effect of pregabalin in middle aged patients after non-cardiac surgery (Agarwal *et al.* 2008; Freedman and O'Hara 2008; Bockbrader *et al.* 2010 Burke and Shorten; 2010 Buvanendran *et al.* 2010). Our finding was also clear: the total parenteral oxycodone during the 16 hours following extubation was reduced by 44% and the total consumption of oxycodone from extubation to the end of the fifth day decreased by 48% in the pregabalin group.

Multimodal or balanced analgesia, the combination of non-opioid analgesic to opioid, has been proposed to decrease opioid like morphine or oxycodone consumption and to improve postoperative pain management after surgery (Kehlet and Dahl 1993). However, most studies have not documented a decrease in the adverse effects of opioids related to the reduction in postoperative opioid requirement (Remy *et al.* 2005). Marret et al. published a meta-analysis, which showed

the benefits of combining NSAIDs and morphine to decrease opioid-related side effects such as PONV and sedation but not pruritus, urinary retention, or respiratory depression (Remy *et al.* 2005). Our result might demonstrate that the opioid-sparing effect of pregabalin reduces postoperative confusion on the first postoperative day. On the contrary, previous studies indicated that the administration of pregabalin was associated with a higher risk of early postoperative sedation and confusion after orthopedic surgery (Mathiesen *et al.* 2008; Buvanendran *et al.* 2010) and increased the incidence of the adverse effects after laparoscopic hysterectomy (Jokela *et al.* 2008b).

The target of multimodal analgesia is not only the improved quality of postoperative pain management, but it is also important to reduce opioid-related side-effects (Kehlet and Dahl 1993). Pregabalin has been shown to reduce the consumption of opioids and pain intensity and to improve postoperative analgesia, but the real clinical benefit is still unclear in a multimodal acute postoperative analgesia. There are also some studies where gabapentinoids have not been beneficial for postoperative pain management (Jokela *et al.* 2008a; Peng *et al.* 2010; Rapchuk *et al.* 2010). Pregabalin is a new-comer in a multimodal analgesia that is yet to play a central role in postoperative analgesia.

9.8.1. THE SIDE-EFFECTS OF PREGABALIN IN ELDERLY

The use of pregabalin has rapidly become a popular analgesic for acute and chronic pain in the elderly. Unfortunately, most studies on pregabalin have been performed in middle-aged patients or in healthy volunteers. Moreover, pregabalin is considered to be a safe drug, although it has remarkable central nervous system-related side-effects for which the mechanism of action is not clear. Pregabalin may have some significant pharmacodynamic interactions. An additive effect of pregabalin with oxycodone has been reported. Also, pregabalin potentiates the effects of lorazepam (Ben-Menachem 2004). In the current study, one patient in the pregabalin group required naloxone for respiratory depression after extubation in the ICU.

In two case studies, patients demonstrated clinical evidence of worsening heart failure and weight gain after pregabalin administration (Murphy *et al.* 2007; Page *et al.* 2008). Possible, interaction with calcium channels may explain the deterioration in heart failure. Furthermore, direct renal effects promoting salt and water retention may also be responsible (Murphy *et al.* 2007). In this study, patients with left ventricular failure or renal insufficiency before the operation were excluded; no patients in the pregabalin group developed heart failure after the operation. Pregabalin can cause nervous system-related adverse effects such as dizziness and somnolence. In this study, all of the patients with stroke were in the pregabalin

group and the incidence of stroke was 8.6%. Stroke incidence after cardiac surgery varies from 1.5 to 9% (Murkin 1999; McKhann *et al.* 2006; Parlow *et al.* 2010). Thus, the finding of incidence of stroke in the present study is comparable with previous studies. Nevertheless, the observation of three strokes in the pregabalin group must be considered seriously.

9.9. POSTOPERATIVE PAIN IN ELDERLY AFTER CARDIAC SURGERY

This is the first study to have indicated decreased pain intensity three months after cardiac surgery due to perioperative treatment with pregabalin. Perioperative treatment with gabapentioids has already been shown to reduce the incidence or severity of chronic postsurgical pain in middle-aged patients after non-cardiac surgery (Fassoulaki *et al.* 2005; Fassoulaki *et al.* 2006; Buvanendran *et al.* 2010). Risk factors for chronic pain after cardiac surgery include a poor acute pain control and a younger age (Bruce *et al.* 2003; Kehlet *et al.* 2006; Lahtinen *et al.* 2006; Taillefer *et al.* 2006; Katz and Seltzer 2009). The incidence of pain three months after surgery was low in this study, being 16% in the placebo and 4% in the pregabalin group. However, the present study was not powered to detect differences in the incidence of chronic pain after surgery. Given their obvious effectiveness, the gababetinoids may play a future role as a component of preemptive multimodal acute pain treatment to increase the effectiveness of the other analgesics and they might also prevent the development of chronic pain.

10. LIMITATIONS OF THE PRESENT SERIES OF STUDIES

The results of these studies must be interpreted with caution due to some limitations.

10.1. SAMPLE SIZE, RANDOMIZATION, AND POWER ANALYSIS IN STUDIES I-V

The study group sample size in the first two studies was small. This prevents the establishment of any conclusions regarding the reasons behind our obtained significant correlations. Power analysis was not done in studies I-II, whilst studies I-III were not truly randomized. The patients of studies I-II were chosen at random based on clinical aspects. Patients were allocated to study groups according to the heart operation number of the clinical computer list in study III. A significantly larger patient population would have been needed for reliable evaluation of confusion, nausea, vomiting, or the incidence of postoperative pain in study V.

10.2. PAIN MEASUREMENT IN STUDIES I-III

The correlations between the different pain tools have to be interpreted with caution because VRS is a verbal tool and the others are visual tools.

10.3. DETERMINATION OF FENTANYL AND OXYCODONE CONCENTRATIONS IN PLASMA

The lower limits of quantitation were set at 1.0 and 2.0 ng/ml for fentanyl and oxycodone, respectively. Probably, due to very low plasma concentrations, a greater sensitivity and the accurary of the determination method for the opioids would have allowed a more detailed pharmacokinetic analysis.

11. CLINICAL ASPECTS

Despite the development of many pain measurement tools in the last twenty years, poor pain management in the elderly remains an issue. Furthermore, there is no universal pain scale that is suitable for all elderly patients. Therefore, pain scales should be evaluated and validated in different types of patients and in different cultures in the future and the most reliable pain measurement tool should be used to relieve pain in a more specific manner. Additionally, the evaluation of pain scales should be a continuous process in the clinical setting. This study suggests that the VRS is appropriate for the assessment of pain intensity of Finnish elderly, even when their cognition is mildly or moderately impaired.

Poor documentation of pain intensity before and after the administration of pain medicine remains a clinical problem in pain management. As long as the recording of pain intensity is incomplete, the quality of pain treatment is insufficient even when the pain scale is validated. In the future, out-hospital patients could potentially self-report their pain intensity, electronically in real time, to the hospital pain monitoring system and database, which could automatically or semiautomatically adjust pain treatment. However, the least healthy elderly will always need the nursing staff, who assess and record their pain systematically using validated pain scales. To improve the clinical management of pain, it is important to implement further quality assurance efforts. Pain intensity and individual therapeutic goals should be defined for each elderly patient. In addition, particular attention must be given to individual dosing of opioids in elderly surgical patients, who often need a smaller amount for adequate analgesia than middle-aged patients.

The elderly population consumes the greatest proportion of prescribed medicines in Western Europe. However, most clinical pharmacological studies have been performed in healthy volunteers or middle-aged patients. Aging causes physiological changes that have an influence on the pharmacokinetics and the pharmacodynamics of drugs, increasing the risk of side effects and drug interactions. In principle, a new drug may cause unexpected effects in the elderly. Therefore, in the future, the elderly should be included in clinical trials more often.

This study indicates that pregabalin might be a new alternative as analgesic for acute postoperative and chronic pain management in the elderly. Its clinical role and safety remains to be verified in large-scale randomized and controlled studies.

12. SUMMARY AND CONCLUSIONS

1. Cognitive dysfunction and depression were associated with reduced daily activities more than chronic pain in home-dwelling elderly people.

2. The scoring of visual pain measurement tools with RWS, FPS and VAS seems to be feasible in elderly patients with a normal cognitive dysfunction. VRS appeared to be applicable in the elderly with a clear evident cognitive dysfunction (MMSE < 17). Immediately after cardiac surgery, VRS proved to be the most feasible pain scale, followed by RWS. The usefulness of VRS for pain assessment in the temporarily confused elderly patients after cardiac surgery and demented patients was shown in this study. The VRS is an easily applicable pain measurement tool for regular assessment in the elderly at the various levels of health care from acute postoperative care to the geriatric department of a primary care hospital.

3. Elderly patients after cardiac surgery had less pain and they needed oxycodone hydrochloride boluses more infrequently and were more deeply sedated than the middle-aged cardiac surgery patients. It is likely that elderly patients are more sensitive to opioid effects. Therefore, particular attention needs to be paid to the dosing of opioids and the regular pain assessment after pain treatment in elderly surgical patients, who often need smaller amounts for adequate analgesia than middle-aged patients.

4. Pregabalin reduced oxycodone consumption, pain and postoperative confusion after cardiac surgery in elderly patients. Pregabalin may be a useful drug for multimodal analgesia for postoperative pain management of the elderly.

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Anne Pesonen

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15. ORIGINAL PUBLICATIONS

1. Kauppila T, Pesonen A, Tarkkila P, Rosenberg PH. Cognitive dysfunction and depression may decrease activities in daily life more strongly than pain in community-dwelling elderly adults living with persistent pain. Pain Practice 2007; 7: 241-7.

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